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VOLUME 75
1945

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO, ILL.

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HISTOPLASMOSIS IN MAN

REPORT OF SEVEN CASES AND A REVIEW OF SEVENTY-ONE CASES

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Histoplasmosis for many years was believed to be a rare tropical disease. Twenty years elapsed between the description by Darling¹ of 3 cases which he had found in 1905 and 1906 and the next diagnosis, which was made by Riley and Watson² in 1926. During the past decade the disease has been found widespread in the United States and in widely scattered places throughout the world. As an indication of the frequency of occurrence of histoplasmosis we have the fact that 9 cases originating in Michigan were discovered between November 1938 and December 1940.

It is the purpose of this paper to report the 5 cases of histoplasmosis which have been observed at the University of Michigan Hospital, 1 case that originated in Ohio but was diagnosed in the Department of Pathology of the University of Michigan, and 1 case that was diagnosed by Dr. Paul Steiner of the department of pathology of the University of Chicago. Brief mention will be made of several cases which have not yet been published and the available literature will be reviewed with particular reference to the clinical aspects of the disease.

Darling was the first to describe histoplasmosis as a disease. Working in Panama, he found his first case in December 1905,^{1a} and 2 more cases during 1906.^{1c} While Strong³ has sometimes

been credited with describing the first case of the disease, he himself⁴ at present is of the opinion that the case which he described was one of those unusual instances of the infection of man with *Cryptococcus farciminosus*, the fungus causing epizootic farcy in horses.⁵ Darling characterized the disease as one in which there were irregular fever, emaciation and splenomegaly. Small encapsulated organisms resembling Leishman-Donovan bodies could be found in the tissues, particularly in the cells of the reticuloendothelial system.⁶ He described the organism as a protozoon and named it *Histoplasma capsulatum*. Sections from Darling's cases were studied by Rocha-Lima⁷ in 1912, and it was his opinion that the organism was a yeastlike fungus rather than a protozoon, a fungus which, as seen in the tissues, closely resembled *Cryptococcus farciminosus*. Confirmation of the fungous origin of the disease did not come until 1932, when DeMonbreun⁸ succeeded in growing the causative fungus from the blood stream and the spleen of a 5 month old infant. Hansmann and Schenken⁹ had culti-

3 Strong, R. P. A Study of Some Tropical Ulcerations of the Skin with Particular Reference to Their Etiology, *Philippine J. Sc.* **1** 91 (Jan.) 1906.

4 Strong, R. P. Personal communication to one of us (C. Z.).

5 Nègre, L., and Bridre, J. Un cas de lymphangite épizootique chez l'homme. Traitement et guérison par le "606," *Bull. Soc. path. exot.* **4** 384 (May) 1911.

6 Darling, S. T. The Morphology of the Parasite (*Histoplasma Capsulatum*) and the Lesions of Histoplasmosis, a Fatal Disease of Tropical America, *J. Exper. Med.* **11** 515 (July) 1909.

7 da Rocha-Lima, H. Beitrag zur Kenntnis der Blastomykosen. Lymphangitis epizootica und Histoplasmosis, *Centralbl. f. Bakt. (Abt. 1)* **67** 233, 1913.

8 DeMonbreun, W. A. The Cultivation and Cultural Characteristics of Darling's *Histoplasma Capsulatum*, *Am. J. Trop. Med.* **14** 93 (March) 1934.

9 Hansmann, G. H., and Schenken, J. R. A Unique Infection in Man Caused by a New Yeast-Like Organism, a Pathogenic Member of the Genus *Sepedonium*, *Am. J. Path.* **10** 731 (Nov.) 1934. A Unique Infection in Man with a New Yeast-Like Organism, *ibid.* **9** 925 (Nov.) 1933.

From the Department of Pathology and the Department of Medicine, University of Michigan Medical School.

1 Darling, S. T. (a) A Protozoan General Infection Producing Pseudotubercles in the Lungs and Focal Necrosis in the Liver, Spleen and Lymph Nodes, *J. A. M. A.* **46** 1283 (April 28) 1906, (b) Notes on Histoplasmosis. A Fatal Disorder Met with in Tropical America, Maryland M. J. **50** 125 (April) 1907, (c) A Fatal Infectious Disease Resembling Kala-Azar Found Among Natives of Tropical America, *Arch. Int. Med.* **2** 107 (Sept.) 1908.

2 Riley, W. A., and Watson, C. J. (a) Darling's Histoplasmosis in the United States. The Possibility of Further Occurrence of Cases, *Minnesota Med.* **9** 97 (Feb.) 1926, (b) Histoplasmosis of Darling. Case Originating in Minnesota, *Am. J. Trop. Med.* **6** 271 (July) 1926.

vated the organism in another case a few months earlier. They mentioned that the fungus resembled *Histoplasma capsulatum* but suggested that it be classified in the genus *Sepedonium*.

Histoplasma capsulatum occurs in the tissues in the form of small round or oval yeastlike bodies, which in our cases have measured from 1 to 5 microns in cross section, the average being approximately 3 microns. Similar measurements have been found by others.¹⁰ They show a sharply defined, clear, achromatic capsule. The chromatin mass in the center of the organisms is irregular in distribution,⁶ and in ordinary stains it usually shows a round vacuole located in the widest part of the cell. The chromatin mass, exclusive of the capsule, measures 1 to 3.3 microns.¹¹ The organisms stain well with most common nuclear dyes, hematoxylin and eosin, the Masson trichrome stain and the Giemsa stain are among the best combination stains for identifying them in tissues, Giemsa and Wright stains as well as supravital stains are satisfactory for staining the organisms in the peripheral blood or sternal bone marrow. The organisms are weakly gram-positive and slightly acid-fast. This is stated thus because with each of these techniques great numbers of the organisms are completely decolorized.¹²

The organism will grow on most of the usual mediums, but since it grows slowly it is frequently difficult to isolate from contaminating organisms. On mediums which contain considerable protein, such as blood or serum agar and Loeffler's medium, inoculation of the yeastlike form results in growth of the yeastlike form if incubation is at 37 C. At room temperature the fungus rapidly reverts to the mycelial form on all culture mediums.⁸ DeMonbreun found that he could not convert a well established mycelial form of the fungus to the yeastlike form by cultural means,⁸ but Conant¹³ has found that by inoculating the mycelial form on a tightly sealed blood agar slant and incubating at 37 C, conversion to the yeastlike form is brought about. Conversion of the mycelial to the yeastlike form was brought about by Negroni¹⁴ by culture of

the mycelial form on blood agar after previous incubation at 37 C in weak solutions of sodium hydroxide (0.01 to 0.05 per cent) or sodium borate (0.5 to 2 per cent). Conversion of the mycelial form to the yeastlike form is accomplished easily by injection of the former into any one of several laboratory animals, i. e., dogs and monkeys,⁵ guinea pigs,¹⁴ mice,¹⁵ rats⁹ and rabbits.¹⁶ In animals, an acute or chronic, localized or widely disseminated infection is produced by varying the dose injected and the route of administration.¹⁵

The infection manifests itself in many different ways, as evidenced by the following case reports and the subsequent review of the literature.

REPORT OF CASES

CASE A (case 24, table)—E. G., a 63 year old white Swiss-born waiter, who had lived in Detroit, Mich., for many years, had apparently been well until January 1938. He then noted the onset of loss of weight associated with extreme nervousness. There had been no chills, fever, sweats, hemoptysis or pain in the chest, but dyspnea occurred with slight exertion. Occasional cough was attributed to postnasal drip. In June a diagnosis of diabetes mellitus was made. Treatment was instituted, but loss of weight continued, with a decline from 190 to 120 pounds (85 to 54 Kg.) by the time he was seen in the outpatient department of the University Hospital on Sept. 29, 1938.

On physical examination the patient was found to be emaciated, poorly developed and acutely ill. The temperature was 99 F., the pulse rate 88, the respiratory rate 20 and the blood pressure 120 systolic and 70 diastolic. The skin was warm, dry and dehydrated. A small, well healed perforation of the nasal septum was seen. The lips were cyanotic, dry and cracked. Oral hygiene was poor, the breath was foul, and the remaining teeth were carious, with marked pyorrhea alveolaris. The pharynx and tonsils were hyperemic and covered with thick whitish exudate. The patient complained of pain on talking and when the tongue was depressed. There was tenderness over the tonsillar and laryngeal areas. A small lymph node was palpable in the right posterior cervical region. The thorax was strikingly emphysematous, and moist, squeaky rales were heard on auscultation. The liver was palpable 5 fingerbreadths below the right costal margin and the spleen 2 fingerbreadths below the left. Tremor of the hands, cyanosis of the nailbeds and a mild bilateral foot drop were present. The reflexes were slightly hyperactive.

The results of laboratory studies were as follows. The Kahn reaction of the blood was negative. The

10 (a) Dodd, K., and Tompkins, E. H. A Case of Histoplasmosis of Darling in an Infant, *Am J Trop Med* **14** 127 (March) 1934. (b) Darling⁶. (c) Hansmann and Schenken⁹.

11 (a) Crumrine, R. M., and Kessel, J. F. Histoplasmosis (Darling) Without Splenomegaly, *Am J Trop Med* **11**:435 (Nov.) 1931. (b) Darling⁶. (c) Case D of this paper.

12 Parsons, R. J. Experimental Histoplasmosis in Mice, *Arch Path* **34** 229 (July) 1942.

13 Conant, N. F. Cultural Study of Life Cycle of *Histoplasma Capsulatum*, Darling 1906, *J Bact* **41** 536 (May) 1941.

14 (a) Negroni, P. Estudio micologico del primer caso sud-americano de histoplasmosis, *Rev d Inst bact*, Buenos Aires **9** 239 (June) 1940. (b) Redaelli, P., and Ciferri, R. Studi sull' *Histoplasma capsulatum*, Darling I. Riproduzione sperimentale della istoplasmosi e definizione della malattia nelle reticolo-istocitosi parassitarie sistemiche, *Bol Soc ital d biol sper* **9** 1001, 1934.

15 Tager, M., and Liebow, A. A. Observations on Histoplasmosis Induced Infection in the Mouse, *Yale J Biol & Med* **14** 469 (May) 1942. De Monbreun⁸ Parsons¹².

16 Hansmann and Schenken⁹ Redaelli and Ciferri^{14b}.

hemoglobin content varied from 70 to 84 per cent (Sahli), the red blood cells from 4,110,000 to 4,930,000 per cubic millimeter, and the white blood cells from 3,400 to 5,900 per cubic millimeter. A typical differential count showed 57 per cent polymorphonuclear neutrophils, 3 per cent eosinophils, 24 per cent large lymphocytes and 16 per cent monocytes.

On four occasions albuminuria (1 to 2 plus) was noted. There was no glycosuria on five examinations. Terminally the urinary sediment was loaded with granular casts.



Fig 1—A large mononuclear phagocyte heavily parasitized by the yeastlike form of *Histoplasma capsulatum*. The section was made from one of the adrenals in case A (case 24 in the table) (Hematoxylin and eosin, $\times 1,860$)

Röntgenograms of the chest showed what appeared to be a tuberculous infiltration of the left upper pulmonary field and involvement of both upper pulmonary fields by minute parenchymal infiltrations, suggesting a lesion of miliary type. Acid-fast organisms typical of *Mycobacterium tuberculosis* were found in the sputum. The total serum protein was 6.6 Gm per hundred cubic centimeters, with 2.9 Gm albumin, and 3.7 Gm globulin. A dextrose tolerance test showed a curve of diabetic type. A faint trace of dextrose was present in the specimen of urine taken at the third hour. On the day of the patient's death the fasting blood sugar content was 121 mg per hundred cubic centimeters and the nonprotein nitrogen content 103.4 mg.

The patient was treated in the outpatient department until the positive result of examination of the sputum was reported, on October 18, when he was admitted as an inpatient. His condition rapidly became worse. Throughout his hospitalization his temperature was intermittently elevated, ranging from 98 to 102.8 F. Swallowing became extremely difficult and painful, finally necessitating intravenous administration of fluids. After the development of cyanosis and coma, death occurred on November 25.

The pertinent observations at necropsy were as follows. There was extensive fibrocascous tuberculosis with cavity formation in the upper lobe of the left lung. Great numbers of tubercle bacilli were readily stained in the walls of the cavities. Miliary tubercles were found in the pituitary gland, thyroid, tongue, pharynx, larynx, lungs, bronchial lymph nodes, kidneys, prostate and small intestine. The liver weighed 1,540 Gm and contained many miliary tubercles. The spleen weighed 470 Gm and histologically showed great numbers of relatively recent miliary tubercles. The kidneys

weighed 170 and 180 Gm and showed relatively acute patchy tuberculous nephritis.

The adrenals were greatly enlarged, one weighing 50 and the other 60 Gm. There was almost complete caseation necrosis of both. The granulation tissue surrounding the areas of caseation necrosis and in the periadrenal fat consisted of young fibroblasts in the meshes of which were many large mononuclear phagocytes. The cytoplasm of these phagocytes contained round or oval bodies (fig 1) measuring from 2 to 5 microns in diameter. Stained with hematoxylin and eosin, these bodies showed a clear achromatic capsule within which was an oval, weakly basophilic chromatin mass. In most instances an almost spherical, clear vacuole could be seen in the chromatin mass. The vacuole was eccentrically placed, but in those organisms which were oval or pyriform it was located in the widest part of the yeastlike cell. The organisms were slightly acid-fast and alcohol-fast and weakly gram-positive.

There was a punched-out ulcer on the tongue 1 cm in diameter. An ulcer in the hypopharynx measured 2.5 by 0.6 cm and was 3 mm deep. From the ileocecal valve to the rectum there were approximately twenty punched-out ulcers, 8 to 12 mm in diameter. A few *Histoplasma capsulatum* organisms were found in macrophages in the granulation tissue base of ulcers in each of these regions.

Extended search for similar organisms in all of the other organs of the body proved futile. None were found in the miliary tubercles, which were widely disseminated throughout the body. Carefully controlled acid-fast stains failed to reveal anything resembling *Mycobacterium tuberculosis* in these tubercles or in the caseous adrenal glands. No cultures were made of the adrenal tissue, and postmortem cultures of blood showed no significant growth.

A diagnosis of histoplasmosis of the adrenals was made on December 1, but it was not until several months later that the organisms were found in the

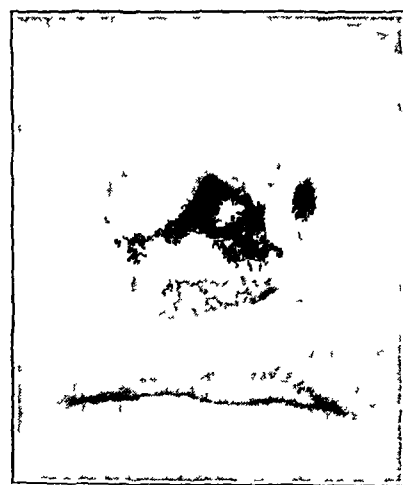


Fig 2—Ulcerated granulomatous lesion in case B (case 37 in the table). The granuloma had caused perforation of the nasal septum. Histoplasmosis was diagnosed by biopsy and by culture of the lesion ($\times 1$)

glossal, pharyngeal and colonic ulcers. Since fibrocascous tuberculosis with cavity formation was present in the lungs, the pathogenesis of the widespread miliary tubercles remains obscure. Neither *Histoplasma capsulatum* nor *Mycobacterium tuberculosis* could be stained in these lesions.

CASE B (case 37 table)—N. C., a 25 year old white woman, a native of Michigan, was admitted to the University Hospital on Aug 30, 1939, with hem-

orrhage from the rectum as the chief complaint. She had been seen there previously, in 1935, at which time a diagnosis of Cushing's syndrome was made.

One year prior to readmission she noted swelling and ulceration of the nose. Septal perforation resulted in two months, but thereafter the lesion was apparently stationary. A purulent, foul-smelling discharge was present continuously. On June 1, 1939, a large amount of blood was expelled by rectum, and several similar episodes occurred subsequently. Weakness, dyspnea and generalized abdominal discomfort followed the repeated hemorrhages.

Physical examination revealed an obese female who appeared chronically ill. The temperature was 99.6 F, the pulse rate 108 and the respiratory rate 16 per minute. The blood pressure was 138 systolic and 94 diastolic. The classic signs of Cushing's syndrome, except the severe anemia, were present. A granulating ulcerative process had partially destroyed the right naris (fig 2). This lesion extended onto the upper lip, and a septal perforation was present with slight involvement of the mucous membrane of the left naris. A purulent exudate could be seen on the ulcerated sur-

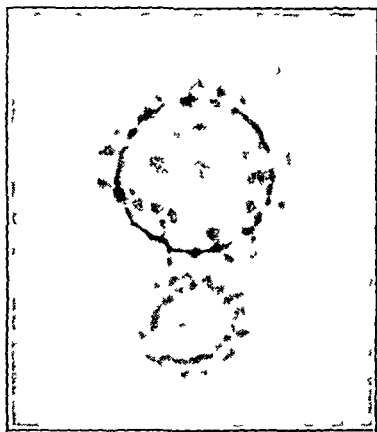


Fig 3—Characteristic tuberculate chlamydospore of the mycelial form of *Histoplasma capsulatum*. The two chlamydospores illustrated were from a culture of the organism from case B. The fungus had been grown on dextrose-tartaric acid medium. Unstained, $\times 1,860$.

faces. Several ulcerations about the gums and one on the roof of the mouth were also seen. There was no palpable lymphadenopathy, and the liver and spleen could not be felt.

The laboratory findings included a negative Kahn reaction of the blood. There were 1,100,000 red blood cells per cubic millimeter, and the hemoglobin content was 20 per cent (Sahli). The white blood cell count was 2,200 per cubic millimeter, and the differential count, 69 per cent neutrophils, 27 per cent lymphocytes and 4 per cent monocytes. Leukopenia persisted throughout the period of observation. Roentgenographic studies of the chest and the gastrointestinal tract did not reveal anything abnormal, nor did sigmoidoscopic examination. Histologic examination of a specimen from the nasal lesion revealed granulomatous tissue containing enormous numbers of large mononuclear phagocytic cells filled with organisms morphologically similar to *Histoplasma capsulatum*, and a diagnosis of histoplasmosis was made. On the following day a small amount of tissue was removed from the ulcer for culture. From this material the mycelial form of *Histoplasma capsulatum* was isolated in broth by Dr. Walter Nungester and on dextrose-tartaric acid medium by Miss Helen Pellet. The characteristic tuberculate chlamydospore (fig 3) of the fungus was easily

identified in these cultures. The organisms were not demonstrated in the peripheral blood or sternal marrow, and repeated blood cultures showed no growth.

While the patient was in the hospital, an irregular pyrexia was present, the temperature reaching as high as 102.4 F. Following repeated blood transfusions, her general condition was improved, and she was discharged, no change having occurred in the nasal lesion. Another episode of gross intestinal bleeding occurred shortly thereafter. The patient was followed in the outpatient clinic, where she was treated with weekly injections of 0.3 Gm of neocarsphenamine, no noticeable benefit resulting from four such treatments. This was discontinued, and the patient was advised to take 0.32 Gm of thymol daily. The liver was easily palpable at this time. She did not return to the hospital during the month before her death, on Nov 21, 1939. While she was at home there had been no further gross intestinal hemorrhage, and although the nasal lesion appeared improved, the lesions of the gums and mouth had become worse. Permission for autopsy was not obtained.

CASE C (case 47, table)—A. J. W., a 41 year old white American salesman, was admitted to the Thomas Henry Simpson Memorial Institute of the University of Michigan on Aug 6, 1940, with the chief complaints of fever and weakness. He had been well until eighteen months prior to admission, when enlargement of the neck was first noted. Examination by his local physician revealed enlarged lymph nodes in the neck, axilla and inguinal regions. On March 30, 1939, a lymph node in the right supraclavicular region was removed for biopsy. After a series of roentgen ray irradiations, the glands regressed so as to become unnoticeable, and the patient felt well and was ambulatory until June 17, 1940. At that time an infection of the upper respiratory tract developed, which persisted for a week. There were ease of fatigue, weakness and a dry, hacking cough. Shortly thereafter fever, profuse diaphoresis, anorexia and abdominal distention developed and persisted to the time of his admission to the hospital. A loss of weight of 30 pounds (13.5 Kg) occurred during the same interval.

On physical examination the temperature was 101.6 F, the pulse rate 88, the respiratory rate 22 and the blood pressure 116 systolic and 58 diastolic. The patient was well developed and well nourished and appeared subacutely ill. The skin was flushed, warm and moist. A few small posterior cervical lymph nodes were felt. A single discrete, soft, nontender node was felt in each axilla, and several inguinal nodes were palpable. The thorax was symmetric and expanded equally on the two sides. The lungs were resonant throughout, but on auscultation the breath sounds were harsh and bronchial in quality. Rales were present throughout, sharp, high-pitched squeaks were heard in the right lower pulmonary field posteriorly on deep inspiration. The abdomen was distended, and there was considerable tenderness in the right upper quadrant. The liver extended 7 cm below the costal margin, and the spleen was palpable 3 cm below the left costal margin.

Laboratory studies gave the following results. The Kahn reaction of the blood was negative. The hemoglobin content declined from 85 to 75 per cent, while the red blood cell count fell from 5,000,000 to 4,000,000 per cubic millimeter, the white blood cell count ranged from 2,650 to 9,550 per cubic millimeter. A representative differential count showed 76 per cent polymorphonuclear leukocytes, 1 per cent eosinophils, 16 per cent lymphocytes and 7 per cent monocytes. On the day of death the reticulocytes numbered 65 per cent, and 1 of every thousand red cells was nucleated. Five analyses of

the urine and two of the stool gave essentially negative results

A microscopic section, prepared at another hospital, from the lymph node removed in 1939 was examined by the department of pathology. A diagnosis of lymphoblastoma of lymphosarcoma type was made, confirming the diagnosis previously made at the other hospital.

Roentgenograms revealed hilar parenchymal changes compatible with the clinical diagnosis of lymphoblastoma. Reexamination of the chest two days before the patient's death showed a considerable increase in the prominence of each hilar shadow and disseminated patchy infiltration of both lungs. It was thought most probably to be due to advance of the lymphoblastoma, although the roentgenologist stated that a disseminated bronchopneumonia associated with extensive lymphadenopathy could produce a similar picture.

During his stay in the hospital the patient became progressively worse. His temperature was irregularly elevated to almost 104 F daily, but during the last four days it fell to near normal levels. The pulse and respiratory rates showed a gradual and continual rise. Roentgen therapy was instituted, the patient receiving 400 r to each of eight ports about the chest and retroperitoneal region without appreciable symptomatic change. Weakness became more pronounced, patchy consolidation of the lungs developed and death occurred on Aug 26, 1940.

After a necropsy a review of the daily blood films revealed the presence of the characteristic yeast form of *Histoplasma capsulatum* in the blood films made during the last two days of life, but not in those made on previous days. The organisms were found in many of the polymorphonuclear leukocytes (fig 4) and could not be found in the other white blood cell elements.

At necropsy the external features were much as described. Moderate edema was present in the feet.

The lungs were more voluminous than usual, the left weighing 950 Gm and the right 1,070 Gm. The pleural surfaces were smooth, moist and shiny except at the apexes, where depressed gray scars were present. The parenchyma was firm but somewhat aerated in spite of the firmness. The cut surfaces were grayish red and firm. On pressure some edema fluid exuded from the surface and grayish mucoid material was found in the bronchi. No tumor masses could be made out. There was slight congestion of the bronchial mucosa. The anthracotic pigmentation of the bronchial lymph nodes in some places gave way to grayish-red streaked areas, but there was no notable enlargement of these nodes. Microscopically, lung sections stained with hematoxylin and eosin and with the Masson trichrome stain showed a widespread subacute pneumonitis. This was characterized by the presence of polymorphonuclear cells, large mononuclear phagocytes and masses of old fibrin in the alveoli. The large mononuclear phagocytes contained numerous small encapsulated organisms morphologically like *Histoplasma capsulatum*. Many of the alveoli were lined with a single layer of flattened cells which could be easily distinguished from the endothelium of the capillaries in the alveolar walls. Organisms were not found in these cells. In a few places organization of the alveolar exudate was seen. Other areas gave evidence of chronic pulmonary edema, and in still others there were acute pulmonary abscesses in which postmortem colonies of cocci were interspersed with the fibrinopurulent exudate. There was hyalinization of dense fibrous pleural and parenchymal scars in the apexes. The bronchi and bronchioles showed an acute fibrinopurulent exacerbation of a chronic bronchitis.

Microscopically, the bronchial lymph nodes revealed an almost complete loss of the usual follicular archi-

tecture. The peripheral sinuses and the sinusoids were packed with large mononuclear phagocytes parasitized by great numbers of small encapsulated organisms, and similar cells were seen in the capsule of the nodes. There were numerous areas of necrosis surrounded by heavily parasitized phagocytes and fibrous connective tissue in the nodes. Apparently inactive fibrocascous tubercles also were present.

The liver was nearly twice the normal size, weighing 2,960 Gm. Its capsule was everywhere smooth and glistening. The yellowish color of the cut surface suggested lipidosis. Microscopically, the liver showed far advanced fatty infiltration. In many of the portal spaces there were small lymphocytes in increased numbers, and some were widened by these cells together with a few large mononuclear phagocytes. The latter contained *Histoplasma capsulatum* in their cytoplasm. In one area this type of cellular infiltration appeared to extend beyond the bounds of the portal spaces into the hepatic parenchyma. Organisms were found in a few Kupffer cells.

Great enlargement of the spleen had occurred, its weight being 620 Gm. The capsule had a purplish color, and a dark red mottling on a purplish background was seen on the cut surface. The pulp was firm. Microscopic sections revealed evidence of marked

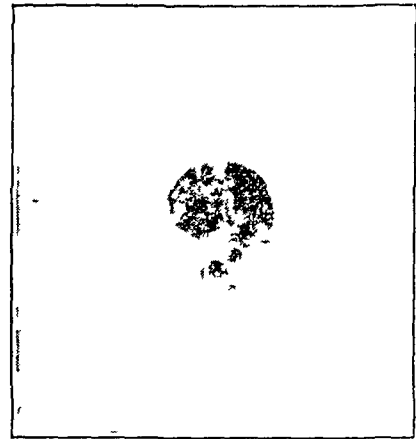


Fig 4—Photograph of a polymorphonuclear neutrophil in a blood smear made in case C (case 47 in the table). Two of the yeastlike forms are seen within the cytoplasm of the neutrophil (Wright's stain, $\times 1,380$).

chronic passive congestion. Parasitized large mononuclear phagocytes were seen singly and in small groups among the lymphocytes in the splenic corpuscles.

Both kidneys were somewhat enlarged, the right weighing 200 and the left 220 Gm. The only apparent gross pathologic change was slight pallor. In sections many of the intertubular capillaries contained large numbers of polymorphonuclear cells and normoblasts.

The adrenal glands were normal in appearance grossly, but microscopically each contained a few parasitized reticuloendothelial cells in the cortical capillaries and sinusoids.

In the region of the ileocecal valve there was hyperplasia of the lymphoid follicles. Large numbers of parasitized large mononuclear phagocytes were seen in this lymphoid tissue. Among the lymphocytes in the gastric mucosa a few parasitized mononuclear cells were present. The same was true of the appendix.

The mesenteric and retroperitoneal lymph nodes were enlarged and revealed small areas of necrosis. They were rather friable. Histologically, the changes in them resembled those described in the bronchial nodes.

The bone marrow from the sternum, a rib and a vertebral body was hyperplastic. A few parasitized

reticuloendothelial cells were found in the bone marrow from a rib and a vertebral body

None of the sections revealed the most remote suggestion of a lymphosarcoma or other neoplasm, and it is our belief that the sections sent us by another hospital which were said to have come from this patient actually were from another patient

CASE D (case 53, table)—D P, a 49 year old white printer, was admitted to the Simpson Memorial Institute on Dec 25, 1940. He had lived in many states during his life, but for the past two years he had lived in the upper peninsula of Michigan. For nine months prior to admission he had noted malaise and anorexia. In June 1940 he experienced severe pain in the right ear which persisted several weeks and then disappeared spontaneously. In August a small nodular lesion appeared in the left external auditory canal. One month later this was incised by his local physician, but no drainage resulted. At that time it was noted that a node in the left preauricular region was enlarged. Subsequently, nonpainful granulomatous oral lesions appeared. During the two month period preceding hospitalization, fever and night sweats became an almost daily occurrence, and there were progressive weakness, malaise and loss of weight.

His local physician took tissue specimens from the lesions of the left ear and the pharynx in December 1940. These were sent to the University of Michigan department of pathology, where the diagnosis of histoplasmosis of Darling was made.

On physical examination, the patient was seen to be well developed but appeared chronically ill and emaciated. His temperature was 98.2 F, his pulse rate 80, his respiratory rate 20 and his blood pressure 88 systolic and 62 diastolic. The skin was loose, revealing evidence of recent loss of weight. On the posterior wall of the right external auditory canal there was a raised granular mass partially occluding the lumen. A similar but larger nodule was present in the left auditory canal. Granulation tissue was present also around a right molar tooth, behind the lower front teeth and on the right posterior tonsillar pillar. The right tonsil was moderately enlarged. The thorax was normal. The abdomen was scaphoid, muscular and difficult to palpate. However, the liver and spleen were each felt 2 finger-breadths below the costal margin. Generalized lymphadenopathy was noted, with involvement of anterior auricular, submaxillary, submental, occipital, anterior and posterior cervical, axillary and inguinal nodes. Some of these nodes were tender.

The laboratory findings included the following. The Kahn reaction of the blood was negative. The red blood cell count was 5,000,000 per cubic millimeters and the hemoglobin content 85 per cent (Sahli). The white blood cell count varied from 4,250 to 5,750 per cubic millimeter, a typical differential count showing 70 per cent polymorphonuclear cells, 3 per cent eosinophils, 18 per cent lymphocytes and 9 per cent monocytes. The total serum protein was 8.2 Gm per hundred cubic centimeters, with 3.9 Gm of albumin, and 4.3 Gm of globulin. The serum bilirubin content was 0.66 mg per hundred cubic centimeters, and the icteric index ranged from 2 to 5. The sedimentation rate was 26 mm per hour (Wintrobe). Sternal aspiration revealed a few extracellular organisms believed to be *Histoplasma capsulatum*. Lymph nodes were obtained for section, animal inoculation and cultural studies. The sections showed many phagocytes filled with *Histoplasma capsulatum*. Young mice were inoculated intravenously with ground suspensions of the lymph nodes. All died with histoplasmosis. Culture of the nodes on blood agar slants at 37.5 C yielded the yeastlike form

of *Histoplasma capsulatum*. Cultures of the nodes on Sabouraud's medium yielded pure cultures of the mycelial form of the same organism. All cultures of the blood were negative. Daily blood films failed to reveal organisms at any time. Roentgen examination of the chest revealed nothing abnormal.

The patient was treated with graduated doses of neostam,¹⁷ a pentavalent antimony preparation, given intravenously. After a total of 0.56 Gm had been administered, this therapy was discontinued because of toxic reactions manifested by nausea, vomiting, severe prostration and what appeared to be an early stomatitis. Sodium thiosulfate in 10 per cent solution was then given intravenously, 10 to 30 cc daily, a total of 14.5 Gm being administered during the course of nine days. Treatment was without avail, and the symptoms present on admission gradually increased. The temperature ranged up to from 99.5 to 101.5 F daily. Within a short period the patient became stuporous, and on Jan 20, 1941, respirations ceased.

At autopsy, peripheral lymphadenopathy such as had been described clinically was present. The peripheral lymph nodes were enlarged to as much as 1 cm in diameter. They were firm and freely movable. In addition, tracheobronchial, mesenteric and retroperitoneal lymph nodes were enlarged to as much as 3 cm in diameter. A few of them showed small, irregular, creamy yellow areas of caseation necrosis.

The right tonsil was moderately enlarged and showed a creamy yellow, chronically ulcerated surface. The remainder of the tonsillar tissue was moist, gray and finely granular in appearance. The mucous membrane of the pharynx, the posterior surface of the tongue, both surfaces of the epiglottis and the mucosa of the larynx showed dome-shaped gray nodules from 1 to 5 mm in diameter and elevated 1 to 3 mm. The central portion of several of these revealed small irregular yellow areas of necrosis. Microscopic sections of these lesions showed a granulation tissue containing great numbers of large mononuclear phagocytes. The phagocytes were heavily parasitized by the yeastlike form of *Histoplasma capsulatum*.

No significant pathologic change was seen in the heart. The lungs were normal in size and shape and weighed 290 and 440 Gm respectively. The right lung, which was the heavier, showed evidences of congestion and edema of the lower lobe. Both lungs had a fine sandy feel to palpation. The cut surface revealed ten to twenty small, firm nodules, 0.8 to 1.0 mm across, which accounted for the sandy texture. The nodules were pale pink. Microscopically, these lesions consisted of irregularly arranged large mononuclear cells lying in a slightly vascular stroma. Numerous lymphocytes were scattered through the lesions. The centers of some of the lesions were the sites of caseation necrosis. However, the lesions did not closely resemble ordinary miliary tubercles. No acid-fast organisms could be found in them, and only one body resembling the yeast form of *Histoplasma capsulatum* was found after extended search. There was chronic catarrhal bronchitis. Anthracosis and an old fibrocaseous tuberculous nodule were found in the bronchial lymph nodes.

The liver was moderately and uniformly enlarged weighing 1,900 Gm. The capsular and cut surfaces showed an unusual mottling, with wide gray-white bands of tissue separating lobules of brown liver parenchyma. Microscopically, the gray-white tissue consisted of bands of young connective tissue which filled the portal spaces, widening and distorting them. Scat-

17 Stibamine glucoside (Burroughs-Wellcome & Co Inc, New York)

tered through this granulation tissue, moderate numbers of lymphocytes and large mononuclear phagocytes were seen. Many of the latter were parasitized by *Histoplasma capsulatum*.

The spleen was slightly enlarged, weighing 205 Gm. The cut surface revealed unusual prominence of the lymphoid follicles. A few of these showed small yellow areas of necrosis. Microscopically, several large mononuclear phagocytes, some of them parasitized, were seen among the lymphocytes in the malpighian corpuscles. At the periphery of some of the malpighian corpuscles, there were milium granulomatous lesions resembling those described in the lungs and containing organisms. Caseation necrosis was present in the largest of these. There was an acute exacerbation of chronic passive congestion.

Extensive pathologic change was present in the adrenals. They were greatly enlarged, the left weighing 70 and the right 65 Gm. The surfaces were mottled gray and white, and each was very firm to palpation. The cut surfaces of each adrenal showed dense gray-white translucent strands of fibrous tissue interspersed between large, irregular, yellow areas of caseation necrosis. No normal adrenal cortex could be found. Study of microscopic sections revealed large mononuclear phagocytes lying at the margins of large areas of caseation necrosis. The phagocytes were very heavily parasitized. The organisms in the phagocytes measured from 1.8 to 4.8 microns, with an average of 2.98 by 3.3 microns, including the capsule. Excluding the capsule the range was 1.35 to 3.3 microns, with average figures of 1.68 by 1.9 microns. Cords of young fibroblastic connective tissue coursed between the areas of caseation necrosis. The adrenal capsule was fibrosed. Parasitized mononuclear phagocytes were present outside and inside the capsule. Only a few small islands of recognizable adrenal cortical tissue could be found, although many blocks of tissue were studied.

The kidneys were normal in size and shape. Microscopically, a few small nodules of granulation tissue of the type that has been described were found in the interstitial tissue. A few organisms were found in these areas.

Large chronic ulcers were found in the mucosa of the small and large intestines. Each of these had a firm, thick, rounded edge and a relatively firm base. The surface of the ulcers was gray and slightly granular. On the peritoneal surface outside the ulcers, there were firm, raised, gray-white fibrous areas. From the margins of these areas, white threadlike strands extended circumferentially beneath the serosa. In the small intestine, the long axis of the ulcers and of the fibrous plaques extended around the intestine and the threadlike strands extended radially toward the mesentery. Microscopically, the base of each ulcer consisted of chronic granulation tissue containing young fibrous connective tissue and parasitized large mononuclear cells. The thin threadlike strands seen grossly were lymphatics which were filled with the same type of granulation tissue. Grossly these ulcers closely resembled tuberculous ulcers, but acid-fast stains failed to reveal any organisms resembling *Mycobacterium tuberculosis*. The ulcers varied from 0.3 to 4.0 cm in their greatest diameter. In the small intestine they were most numerous in the ileum. None was present in the duodenum.

In addition to the changes just described, small granulomatous lesions resembling those described were found in the submucosa of the appendix and in a parathyroid gland.

The yeastlike form of *Histoplasma capsulatum* was easily grown in pure culture from the direct smear of

adrenal tissue on a blood agar plate incubated at 37 C. This was properly identified by growth of the mycelial form of the fungus.

CASE E (case 71, table)—M. K., a 60 year old white American farmer, had been well until October 1942. At that time he noticed a swollen, tender area on the left side of the upper surface of his tongue. The lesion spread down over the side of the tongue to involve the floor of the mouth. Considerable pain was associated with it. About November 1, the upper lip became swollen and painful. The lesions progressed until he entered the University Hospital, Jan 18, 1943.

Physical examination revealed a punched-out, smooth, well circumscribed ulceration on the top of the tongue which measured 2 by 3 cm. The ulcer was extremely tender when touched. Swelling of the entire upper lip was present, and on the left side there was an ulcer 4 by 1.5 cm, just within the vermillion border. This lesion was also exquisitely tender. A palpable lymph node was found in the left submaxillary region. He was edentulous and had worn dentures for twenty years. His weight on admission was 120 pounds (54 Kg), this representing a loss of 15 pounds (7 Kg) during the past few months. The remainder of the physical examination showed no significant variations from normal. The liver and spleen were not palpable. The blood pressure was 120 systolic and 60 diastolic, and the admission temperature was normal.

The laboratory findings during his illness were as follows. The Kahn reaction of the blood was negative repeatedly. A Kahn test of the spinal fluid and a Kline test of the blood also gave negative results. The hemoglobin content ranged from 63 to 67 per cent, and the red blood cell counts varied from 3,800,000 to 4,000,000 and the white blood cell counts from 4,050 to 9,800 per cubic millimeter. A typical differential count was polymorphonuclear neutrophils 74.5 per cent, lymphocytes 14 per cent, monocytes 10 per cent, eosinophils 0.5 per cent and basophils 1 per cent. (This patient had been in the University Hospital in 1940 with herpes zoster oticus. Red blood cell counts at that time ranged from 4,200,000 to 4,380,000 and white blood cell counts from 5,600 to 6,550. Differential counts at that time were not significantly different from that just given.) Repeated careful study of the blood smears, smears of the buffy coat from centrifuged blood and smears of a sternal marrow failed to show *Histoplasma capsulatum*. Vacuolation of the monocytes was noted in one of the blood smears. The urine was essentially normal until early in June, when 3 to 5 red blood cells and 10 white blood cells per high power field and a trace of albumin were found. There were similar urinary findings a few days later. The nonprotein nitrogen content was 42 mg per hundred cubic centimeters and the serum calcium content was 9.3 mg.

A tuberculin test showed a minimal positive reaction forty-eight hours after the intracutaneous injection of a 1:100 dilution of old tuberculin. The reaction to a cutaneous test with 1:1,000 coccidioidin was negative. Cutaneous tests for histoplasmosis¹⁸ gave negative results with dilutions of 1:10,000 and 1:1,000. Agglutination tests for tularemia and undulant fever also gave negative results.

The elevations in temperature were irregular at first. During the first two weeks the temperature was within the normal range on all except two days, when there was an elevation to 102 F. Then the temperature was

18 Zarafonitis, C. J. D., and Lindberg, R. B. Histoplasmosis of Darling. Observations on Antigenic Properties of Causative Agent. Preliminary Report, Univ. Hosp. Bull. Ann Arbor 7:47 (June) 1941.

elevated to 101 or 102 F daily for two weeks. Next, for a period of three weeks, the temperature was in the normal range most of the time and never rose to 100 F. After March 14 there was a daily spiking of the temperature curve, with daily return to normal or below. The peak temperatures were usually 101 or 102 F, but on a few occasions temperatures of 104 and 105 F were attained. Associated with these high temperatures there was frequently a mild chill.

During the patient's first three weeks in the hospital, material was removed from the ulcerated areas of the lip and tongue for histologic examination and for culture and animal inoculation. The first biopsy material showed evidence of a chronic infective granuloma. No organisms were found in the sections. The lesion had many of the attributes of tertiary syphilis. The second biopsy showed the same general characteristics, but this time some of the granulation tissue had a nodose character. Acid-fast stains failed to reveal *Mycobacterium tuberculosis*, but the Giemsa stain revealed a few intracellular yeastlike bodies. These bodies were of much larger size and of different shape than *Histoplasma capsulatum*. The organisms were described and it was stated that they might indicate a form of pathogen with which we were unfamiliar or that they might consist of secondary invaders. *Histoplasma capsulatum* was not seen in other biopsy specimens of the lip and tongue.

Anaerobic and aerobic cultures, cultures for tubercle bacilli and cultures for fungi were made of fresh fragments of tissue at the time of the biopsies just mentioned. These cultures, as well as many others made of smears of the ulcers and of the sputum and urine, all failed to reveal a significant pathogen. Guinea pigs inoculated with fragments of tissue and with concentrated sputum failed to show any evidence of infection.

The lesions of the lip and tongue remained approximately unchanged for several weeks. Granulomatous ulcerations developed in the pharynx and larynx during the early part of March. These were widespread and finally caused extreme dysphagia and complete aphonia. Biopsy and culture of the pharyngeal tissue revealed no clues as to the nature of the process.

Late in March there was evidence of a pneumonitis at the base of the right lung. This cleared after a few weeks, and a similar process developed at the base of the left lung in the latter part of April. A widely disseminated generalized fine granularity of both lungs, more pronounced on the right, was noted in roentgenograms early in April, but it appeared to have retrogressed somewhat by the end of the month.

Many forms of treatment were tried without avail. Mouth washes with potassium permanganate solution, swabbings with tincture of iodine and glycerine and irrigations of the throat with hot saline solution were all used to combat the oropharyngeal ulcerations. Intramuscular injections of a bismuth preparation and oral administration of potassium iodide were used. During a period of one week early in March, 6 Gm of sulfadiazine was given each day. This did not alter the progress of the pharyngeal and laryngeal ulcers. Potassium and antimony tartrate was given intravenously in increasing amounts during two of the last three weeks of life. After the application of 900 r of roentgen radiation to the lesion of the lip and to each side of the neck, there was a subsidence of the extreme tenderness in the labial and pharyngeal lesions. During this treatment, the lesions of the lip and tongue showed considerable regression but failed to heal.

The patient's general condition gradually became worse. There was further loss of weight to 99 pounds (44.5 Kg). The dysphagia became so severe that it

was necessary to perform a gastrostomy. The liver became barely palpable on deep inspiration. Finally several transfusions of whole blood were given. After the last of these the patient appeared to go into shock. The heart rate was irregular, and an electrocardiographic tracing showed many showers of ventricular extrasystoles. Cheyne-Stokes respiration developed, and respirations ceased on July 16, 1943.

An autopsy was done one hour and fifteen minutes after death. There was nothing remarkable on external examination. The left side of the tongue showed a large ulcerated area (fig 5), which measured 4 cm in its greater diameter. The edges of the ulcer were rounded and smooth, while the base of the ulcer was red and smooth in appearance. On the posterior surface of the tongue there were numerous irregular, raised gray nodules which did not appear to be ulcerated. Similar nodules were seen in the mucosa of the pharynx. The tonsils were not remarkable. There was slight thickening of the epiglottis, and a granular, ulcerated area covered much of its laryngeal surface. The entire mucosa of the larynx was thickened, and its surface presented an ulcerated, gray, finely granular appearance. The vocal cords had been almost completely destroyed.



Fig 5—Irregular, punched-out ulcer of the tongue in case E (case 71 in the table). The ulcer measured 4 cm in its greater diameter. *Histoplasma capsulatum*, in the yeastlike form, was found in large mononuclear phagocytes in the base of the ulcer (+1).

by the ulcerative process. The trachea showed no gross pathologic change.

Delicate fibrous adhesions were found in each pleural space. The left lung weighed 380 and the right 520 Gm. A generalized fine nodularity was noted throughout both lungs. A 1 cm, well defined fibrous nodule was found in the upper lobe of the right lung, and a similar nodule was found in a bronchial lymph node. A small atelectatic area was found at the base of the right lung. The bronchi were not remarkable. The bronchial lymph nodes were slightly enlarged. They showed anthracotic pigmentation and were rubbery.

The heart was normal in shape and weighed 320 Gm. The myocardium was flabby and of normal thickness. The chambers were of normal size. On the atrial surface of the leaflets of the tricuspid valve there were three raised, moderately firm, yellowish, verrucous vegetations. The largest of these measured 2 cm in height and protruded into the right ventricle. The other two lesions were sessile. Except at the base of the vegetations there was no thickening of the leaflets. A small fibrous adhesion was found close to the com-

missures of two of the pulmonic cusps. The mitral and aortic valves showed only changes incident to atherosclerosis.

There was no gross abnormality of the spleen, which weighed 140 Gm. The firm liver was slightly enlarged, weighing 1,980 Gm. The mesenteric lymph nodes were not unusual. The kidneys weighed 140 and 150 Gm. The left showed three whitish subcapsular nodules approximately 1 mm in diameter. The remainder of the organs, including the brain and a segment of the spinal cord, were without significant gross changes.

Cultures were made of material from the lesions at the base of the tongue, the ulcerated areas in the larynx and the large vegetation on the tricuspid valve.

Routine sections of the tricuspid vegetation showed large masses of fibrin attached to the ulcerated surface of the tricuspid valve. A few fibroblasts could be seen growing into the base of the vegetation, and a few large mononuclear cells, apparently phagocytes, were seen in the meshes of the fibrin near the base of the vegetation as well as in groups near its surface. No recognizable etiologic agent could be found in the routinely stained sections. However, after sections were stained with Giemsa stain, veritable colonies of small encapsulated yeastlike bodies having the size, shape and staining attributes of *Histoplasma capsulatum* were readily seen. These colonies were found deep in the masses of fibrin and were entirely extracellular. In these colonies a few of the organisms attained a greater size than we have previously seen, the largest being slightly oval and measuring 10.5 by 9 microns. The chromatin mass within the capsule measured 7.5 by 6.5 microns. Numerous budding forms were present. Sections of one of the smaller vegetations showed small colonies of the usual pathogenic form of *Histoplasma capsulatum* surrounded by thick, hyaline masses of fibrin. Some of these colonies were attached to the ulcerated surface of the valve. Others were seen between the collagen fibers of the valve, some distance below a surface that was covered by apparently normal endothelium. There was no evidence of cellular activity about these. At one point, just beneath the endothelium, numerous organisms were seen free in the tissues and not surrounded by fibrin.

Examinations of the lesions on the tongue, in the pharynx, on the epiglottis and in the larynx revealed extensive ulceration of the mucous membrane. The base of the ulcer in each case was formed by granulation tissue which consisted of moderately vascular fibroblastic connective tissue heavily infiltrated with plasma cells and lymphocytes. Protracted examination of this granulation tissue revealed a few large mononuclear phagocytes. The cytoplasm of many of these phagocytes contained one or more *Histoplasma capsulatum* organisms, but they were not present in the great numbers that we had seen in the earlier cases. The organisms were found most easily at the margins of the ulcers, beneath intact epithelium. None was found in the cytoplasm of the plasma cells or lymphocytes. A striking feature of several of these ulcers was the nearly complete lack of polymorphonuclear neutrophils in the granulation tissue forming the base of the ulcers. Mast cells were found in small numbers throughout the granulation tissue.

A few *Histoplasma capsulatum* organisms were found in large mononuclear phagocytes in the leptomeninges over the base of the brain in one section and in the wall of a small meningeal artery. A few were found in the media of the aorta and in the wall of a small adventitial artery of the aorta. These organisms did not appear to be intracellular. In the lungs numerous small nodular lesions were visible to the unaided eye in the sections. Microscopically most of these were seen to consist of

small, irregularly shaped masses of connective tissue which showed heavy anthracotic pigmentation. There were a few sharply circumscribed lesions which consisted of large mononuclear phagocytes surrounded by a narrow band of lymphocytes. A few giant cells were found in the centers of the lesions. These lesions closely resembled true miliary tubercles, but stains for acid-fast bacilli revealed no tubercle bacilli and an occasional *Histoplasma capsulatum* organism was found in the phagocytes and in the giant cells. A few organisms were likewise found in the cytoplasm of alveolar phagocytes. One section showed a whorled fibrous scar which was believed to be the remains of a healed primary tuberculous infection. A similar healed fibrous nodule was seen in a bronchial lymph node. No identifiable organisms were found in the bronchial lymph nodes.

Small granulomatous nodules consisting of young connective tissue, moderate numbers of lymphocytes and plasma cells and a few large mononuclear phagocytes were seen in the liver and pancreas. Minute examination of these lesions revealed an occasional pale acidophilic-staining body having the size and shape of *Histoplasma capsulatum*, but they could not be definitely identified as such. A few *Histoplasma capsulatum* organisms were found in the cytoplasm of a small group of mononuclear cells in the wall of one of the ureters and a few were found in the bone marrow from a rib. No organisms were found in the pancreas, spleen or mesenteric lymph nodes or in the other organs of the body, except those specifically mentioned.

The cultures made at the autopsy failed to yield a growth of *Histoplasma capsulatum* or any other fungus, in spite of the fact that the materials were taken and handled by one thoroughly conversant with the cultural characteristics of *Histoplasma capsulatum*.

After the facts just cited were known, the biopsy specimens were reexamined. Careful search with the oil immersion objective revealed *Histoplasma capsulatum* in each of the slides that had been previously examined. The organisms occurred, for the most part, 1 or 2 within a cell, instead of in the large numbers which we had seen previously, and it was necessary to search one section for an hour before the first organism was found. This experience has taught us that *Histoplasma capsulatum* may be exceedingly difficult to find even in well stained preparations. While in the vast majority of instances hematoxylin, in a hematoxylin and eosin stain, stains the organisms well enough so that they can be identified, on some occasions this method fails. In all instances it would appear to be desirable to search carefully sections stained with the Giemsa or the Masson trichrome method.

CASE F (case 13, table)—A 12 year old boy, who lived in Ohio, suffered from what was considered to be aplastic anemia and was sick for eleven weeks before death. An autopsy was performed, and the essential abnormal condition noted was a generalized lymphadenopathy, especially of the mesenteric nodes. A slide prepared from one of these nodes was sent to the department of pathology in May 1936. A descriptive diagnosis of intracellular parasites was given at that time. After the diagnosis made in case A, this material was reexamined and the markedly hyperplastic reticuloendothelial cells of the lymph node were found to contain many organisms that were morphologically identical with *Histoplasma capsulatum* as it occurs in the tissues. The organisms had been seen but not identified in 1936.

CASE G (case 49, table)—This case is reported here because of its unusual interest. It is published with the permission and approval of Dr. Paul Steiner and Dr. Paul Cannon, of the department of pathology of

Summary of Cases

[illegible]

Author	Year	Sex	Age	Site	Diagnosis	Pathology	Microscopic	Immunologic	Response	Outcome	Comments
1. Al-Ita	1939	Male	10	Illinois	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
2. Anderson	1939	Male	10	Illinois	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
3. Anderson	1939	Male	10	Illinois	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
4. Brown	1940	Male	10	Texas	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
5. Derry	1940	Male	10	England	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
6. Ramsey	1940	Male	10	Michigan	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
7. Parsons	1940	Male	10	Michigan	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
8. Scott	1940	Male	10	Pennsylvania	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
9. Steiner	1940	Male	10	Illinois	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
10. Palmer	1940	Male	10	Michigan	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
11. Poncher	1940	Male	10	Illinois	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
12. Thompson	1940	Male	10	Illinois	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
13. Parsons	1940	Male	10	Michigan	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
14. Hill	1941	Male	10	Texas	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
15. Lawson	1941	Male	10	Tennessee	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
16. Allen	1941	Male	10	Missouri	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
17. Sloman	1941	Male	10	Rhode Island	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
18. Fey	1941	Male	10	Missouri	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
19. Jorstad	1941	Male	10	Missouri	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
20. Lancaster	1941	Male	10	Washington	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
21. Hunter	1941	Male	10	Washington	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
22. Green	1941	Male	10	Missouri	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
23. Briere	1941	Male	10	Oklahoma	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
24. Becker	1941	Male	10	Illinois	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
25. Fiere	1941	Male	10	Louisiana	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
26. Dawson	1941	Male	10	Tennessee	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
27. Colvin	1941	Male	10	Alaska	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
28. Moore	1941	Male	10	Missouri	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
29. Brien	1941	Male	10	New York	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
30. Thomas	1941	Male	10	North Carolina	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis
31. Parsons	1941	Male	10	Michigan	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis	Leishmaniasis

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the University of Chicago Dr Steiner provided us with the data The patient was a white Illinois farmer 56 years of age He became ill in October 1939 There were abdominal pain, vomiting, anorexia, loss of weight, dyspnea, a mass in the abdomen and lymphadenopathy By biopsy of an inguinal lymph node in January 1940, Hodgkin's disease was diagnosed, and the nodes responded well to roentgen therapy Later there was a papular eruption of the skin which was thought due to Hodgkin's disease All the peripheral lymph nodes were enlarged, discrete and nontender Some were as large as a golfball Roentgenographs of the thorax showed widening of the mediastinal shadow The liver could not be felt until terminally, when it was palpable 2 cm below the costal margin The spleen was always palpable 4 to 8 finger-breadths below the costal margin There was no fever early in the illness, but later there was irregular elevation of temperature up to 103 F Toward the end, the pulse rate was 120 and the blood pressure was 110 systolic and 76 diastolic Laboratory findings included red blood cells, 4,400,000 to 3,200,000, hemoglobin, 78, 56 and 70 per cent in successive determinations, white blood cells, 11,300 to 1,400 (terminal), with differential counts of 56 to 62 per cent neutrophils, 23 to 31 per cent lymphocytes, 2 to 10 per cent mononuclear cells, 5 to 7 per cent eosinophils and 1 per cent basophils Later the number of monocytes went up to 12 per cent The urine showed albumin on one occasion, and a positive reaction to a benzidine test was obtained from the stool on one occasion

The autopsy was done by Dr Steiner on Sept 13, 1940 It showed the typical lesions of Hodgkin's disease involving the abdominal lymph nodes, spleen, liver and bone marrow Microscopic examination also revealed the lesions of histoplasmosis in peripheral and visceral lymph nodes, lungs, liver, spleen and bone marrow The kidneys and adrenals showed no organisms Bone marrow from eight different bones was examined, and it was extensively replaced by small areas of necrosis which were surrounded by large mononuclear phagocytes These contained great numbers of organisms which were morphologically identical with *Histoplasma capsulatum* In the bone marrow the lesions of Hodgkin's disease were sometimes separate and sometimes intermixed with the much more extensive lesions of histoplasmosis It was Dr Steiner's opinion that the leukopenia was caused by the replacement of the marrow by the latter lesions It is agreed by the pathologists who have seen the sections from this case that both Hodgkin's disease and histoplasmosis were present The history of the case suggests that Hodgkin's disease came first, but of course this cannot be proved The question must be asked Did Hodgkin's disease, a disease in which cells of the reticuloendothelial system become malignant, predispose this man to histoplasmosis a disease which is characterized by the parasitization of the cells of the reticuloendothelial system by the yeastlike form of the fungus *Histoplasma capsulatum*?

The following are brief notes on a few additional cases which have come to our attention but which have not appeared in the literature as yet

CASE H (case 17, table)—A 68 year old white woman, a patient of Dr Karl O Stingily, Meridian, Miss, who had always lived in Mississippi, was first seen in 1937 with an ulcer on the tongue. Biopsy of the ulcer led to the diagnosis of carcinoma, grade I The lesion was treated with radium and healed One

year later two ulcers appeared, and another biopsy showed extensive infiltration of the base of the ulcer with large mononuclear phagocytes which were heavily parasitized with organisms morphologically the same as *Histoplasma capsulatum* One of us (R J P) has had the privilege of examining the second specimen from this case and of confirming the diagnosis After this second biopsy, the lesions were treated with "superficial" roentgen irradiation and healed At the time of writing, after the lapse of five years, the patient is in good health and shows no manifestations of the disease

The husband of this patient also had a chronic punched-out ulcer on his tongue This ulcer antedated the one in case H by several months, according to Dr Stingily This of course suggests direct contact infection It was not possible to obtain a specimen for biopsy, and the patient died in 1941 Since autopsy was not allowed, proof of the causation of the ulcer is lacking

CASE I (case 60, table)—A 63 year old white man, a patient of Dr Benjamin Manchester, Washington, D C, had splenomegaly and hepatomegaly Toward the end of his illness, in 1941, he showed evidence of adrenal insufficiency He died in spite of treatment with adrenal extract At autopsy there was bilateral adrenal necrosis due to histoplasmosis Organisms could not be found in any other organ of the body The diagnosis of histoplasmosis was confirmed by Colonel Ash, of the Army Medical Museum

CASE J (case 65, table)—The information on this case was sent to us by Dr Edward L Burns, of the Louisiana State University School of Medicine A 55 year old white man, a native of Louisiana, entered the hospital complaining of hoarseness following a "chest cold" There was dysphagia, and ulcers appeared at the angles of the mouth and on the hard palate The aryepiglottic folds were thickened The submental and cervical lymph nodes were enlarged, but the liver and spleen were not enlarged The blood counts were within normal limits The urine showed a trace of albumin The patient died in October 1942 At autopsy disseminated histoplasmosis was found One of us (R J P) chanced to see a section from the larynx in April 1943

REVIEW OF THE PRESENT STATUS OF HISTOPLASMOSIS

A study of the literature of histoplasmosis has been made, and a brief summary of the clinical data and autopsy observations for each case, when such are available, is given in the accompanying table The table includes 6 cases which have been observed at the University of Michigan, 5 of which have previously been mentioned in the literature¹⁹ but not described in detail Also included are the available data on 15 cases which have not yet appeared in the literature Several of these cases will undoubtedly be published, and we are indebted to the physicians concerned with them for the information that they have made available at this time

19 (a) Melcney, H E Histoplasmosis (Reticulo-Endothelial Cytomycosis) A Review with Mention of Thirteen Unpublished Cases, *Am J Trop Med* 20: 603 (July) 1940 (b) Parsons, R J The Histopathology of Histoplasmosis in Man, abstracted, *Am J Path* 17 582 (July) 1941.

INCIDENCE AND DISTRIBUTION OF HISTOPLASMOSIS

For the purpose of giving as accurate an idea as possible of the frequency of histoplasmosis, or at least the frequency of recognition of the disease, the cases in the table have been arranged, as nearly as possible, in the order of their occurrence rather than in their order of publication. In some instances it has been impossible to establish this order accurately, and in these instances we have made as close an approximation as possible.

It will be noted that since 1936 the number of cases of the disease appears to have increased suddenly, so that 15 cases were discovered in 1939 and 12 cases in 1940. Since the distribution of the disease appears to have been worldwide (see following section) over the past three decades, one is tempted to think that the reason for the apparently increased incidence lies in better recognition rather than in a truly increased frequency of occurrence. Indeed 3 of the cases (4, 13 and 21) were properly identified from two to eighteen years after the patient's death. However, if one is to believe that the increase in number of cases is due only to better recognition, it is remarkable that many more cases have not been identified from the literature and from older cases in many laboratories. Search through large numbers of reports of the older complete autopsies at the University Hospital has failed to reveal a single case of histoplasmosis. During the fall of 1938 and the spring of 1939 a total of 4 cases of histoplasmosis was found in Southern Michigan by three pathologists. Each of these pathologists recognized the disease as something new to him, and each arrived independently at the proper diagnosis. Five other cases occurred in Michigan during the next two years, and still another patient died of the disease in July 1943. Similarly, the first case to be found in Nashville, Tenn., was diagnosed in 1932. No more cases were encountered there until 1937, and from 1937 through 1942 one or more cases have occurred each year. It seems most probable that the incidence of the disease is definitely on the increase.

Distribution—Geographic Incidence. The disease is widespread throughout the world. In the various countries, cases have occurred as follows: Austria, British Honduras, East Java, England, Mexico, the Philippines and Southern Rhodesia, 1 case each; Argentina, 2 cases; Brazil and the Panama Canal Zone, 3 cases each, and the United States, 56 cases. The cases in the United States have been distributed as follows: Florida, Iowa, Louisiana, Maryland, Minnesota, Mississippi,

New York, North Carolina, Ohio and Oklahoma, 1 case each; Alabama, California, Kentucky, Texas, Virginia and Washington, D. C., 2 cases each; Indiana, 3 cases; Illinois, 4 cases; Tennessee, 7 cases; and Missouri and Michigan, 10 cases each. It can be seen that more than a third of the cases have occurred in four Midwestern States.

Instead of histoplasmosis being a disease with a tropical distribution as suggested by Darling¹⁴ it is now apparent that it must be looked for in the temperate and subtropical regions of the world as well.

Race. The race to which each patient with histoplasmosis belonged is given in column 5 of the table. Data are available in 63 cases. The disease has been seen in 51 white persons, 7 Negroes, 2 mulattoes, 1 Javanese, 1 Chinese and 1 Honduran.

Sex. Histoplasmosis occurs more frequently in males than in females, as demonstrated by the data in the table. In the 65 cases in which data are available, 51 patients were male and 14 were female. If these figures are broken down further, it is found that up to and including the age of 10 years the incidence is the same in the two sexes, there being 8 patients of each. Of the 49 patients older than 10 years of age, 43 were males and 6 were females.

Age. Every age group is susceptible to infection with *Histoplasma capsulatum*. The table gives the ages of 60 patients in the present series of cases. They are distributed as follows: 0 to 1 year, 11; 1 to 9 years, 4; 10 to 19 years, 3; 20 to 29 years, 5; 30 to 39 years, 5; 40 to 49 years, 11; 50 to 59 years, 10; 60 to 69 years, 9; and 70 to 79 years, 2. The incidence is highest during the first year and then falls off sharply but reaches another peak during the fifth, sixth and seventh decades. The first symptoms of the disease were noted during the second month of life in 3 cases (27, 51 and 66) and possibly during the first month of life in case 64. The oldest patient reported so far is the one in case 56. This patient died at the age of 71 years.

Occupation. The occupations of 30 of the patients in this series who were more than 12 years of age are known. Ten of the 30 were farmers, 4 were laborers, 2 were bartenders and 2 were waiters. There was 1 each of the following types of worker: baker, carpenter, janitor, lawyer, mine manager, printer, salesman, school teacher, soldier, steel worker, student and teamster.

SIGNS AND SYMPTOMS OF HISTOPLASMOSIS

Infection with *Histoplasma capsulatum* is manifested in many different ways. There may

be ulcerative lesions of the skin and/or mucous membranes of the mouth and pharynx. There may be localized or generalized lymphadenopathy. Most of the viscera may be involved (all have been involved in one case or another), or only one organ, such as the adrenal, may be affected. The intestinal tract is frequently the site of ulcerated lesions.

Skin—Of the 61 cases on which there were sufficient data for analysis, in 19 some form of skin lesions were present: ulcers in 9 instances, a papular eruption in 4 (cases 4, 10, 15 and 59), and purpura, usually occurring in the last two or three days of life, in 6. Petechial hemorrhages and bullous lesions were each noted once. Chronic ulcers sometimes occur in the center of the papular lesions. The ulcers are frequently deep, with sharp, steep edges, giving a punched-out appearance. They are well illustrated in the paper of Balñá and associates²⁰. The papular eruption is illustrated in the paper of Hansmann and Schenken⁹.

Ear—The middle ear or the aural canal was the site of lesions in 8 instances. True otitis media was described in 5 of these (cases 11, 25, 42, 52 and 54). In case 11 the organisms were demonstrated in the pus from the middle ear. In case 30 the patient had been treated for a fungous infection of his ear shortly before the onset of generalized symptoms of histoplasmosis.

Eye—Reid and associates,²¹ in case 32, described "small, white irregular areas surrounded by hemorrhage in the ocular fundi. They were not unlike tubercles." Definitive changes in the eyegrounds have not been noted in other cases.

Mouth and Nose—Ulceration of the mucous membrane of the mouth, most frequently of the tongue, was noted in 14 cases. In 4 additional cases there was ulceration of the mucous membrane of the nose as well as of the mouth. In case 64 the patient had ulcerations in the nose but none in the mouth. Perforation of the nasal septum was noted in 3 cases. In cases 14 and 37 the perforation was produced by infection with *Histoplasma capsulatum*. In case 24, the perforation appeared to be well healed and may have had no relation to histoplasmosis. In at least 4 cases (cases 17, 53, 56 and 59) the clinical diagnosis on lesions of the oral mucosa was carcinoma.

Pharynx—Granulomatous and ulcerated lesions were found in the pharynx in 10 instances. The lymphoid tissue in the tonsils and in the mucosa of the pharynx is most frequently the site of the lesions.

Larynx—Granulomatous and ulcerative lesions appeared in the larynx in 10 instances, usually in association with lesions of the pharynx. Aphonia, dysphonia and dysphagia were frequently present with these lesions.

Lymph Nodes—The superficial lymph nodes were enlarged in 29 of the 61 cases that can be analyzed. The enlargement was generalized in 16 instances. The cervical nodes were involved alone in 5 cases and along with another group of regional nodes in 4 additional instances. In 1 instance (case 22) the inguinal nodes alone were enlarged. When the lymph nodes were enlarged, they frequently reached a diameter of 1 to 2 cm or more. They were moderately firm and frequently were freely movable but occasionally were matted together. The nodes were sometimes tender. There was roentgenographic evidence of enlargement of the mediastinal lymph nodes in 4 instances.

Lungs—The findings in the lungs in cases of histoplasmosis are variable, depending on the degree and the type of involvement. In this series, cough was noted as a symptom in 11 cases. Rales of various sorts were mentioned in 13 cases. A friction rub was noted 4 times, and a diagnosis of pneumonia was made at least 8 times. In 11 instances, a diagnosis of tuberculosis had been made or at least seriously entertained before death. The clinical evidence for tuberculosis in these cases had been apical opacities and cavities seen roentgenographically, miliary lesions scattered throughout the lungs, or tubercle bacilli in the sputum. Tubercle bacilli were found in the sputum in 3 instances (cases 24, 35 and 70), while in a fourth (case 34), tubercle bacilli were found in pulmonary lesions at autopsy. Miliary lesions have been found in the lungs on several occasions (cases 24, 34, 35, 53, 67, 69, 70 and 71). No tubercle bacilli could be found in the miliary lesions in case 24 in spite of the presence of pulmonary tuberculosis. In case 53, a single *Histoplasma capsulatum* organism was found in one of the miliary lesions. No tubercle bacilli were found but this was to be expected, since no active tuberculous focus was present. In 5 instances (cases 4, 15, 24, 35 and 70) roentgen examination revealed parenchymal changes which were considered typical of active pulmonary tuberculosis. In cases 4 and 15 there was no mention of tuberculosis at autopsy, while in the other cases typical

20 Balñá, P. L., Negroni, P., Bosq, P., and Herrera, J. A. Histoplasmosis de Darling. Primer caso sudamericano, *Rev. argent. dermatosif.* 25:491, 1941.

21 Reid, J. D., Scherer, J. H., Herbut, P. A., and Living, H. Systemic Histoplasmosis Diagnosed Before Death and Produced Experimentally in Guinea Pigs. *J. Lab. & Clin. Med.* 27:419 (Jan) 1942.

active tuberculous lesions were found along with the lesions of histoplasmosis. Since the signs and symptoms of pulmonary histoplasmosis have frequently been mistaken for those of pulmonary tuberculosis, and especially since the two conditions may exist together, the differential diagnosis will be difficult. The intradermal test for *Histoplasma capsulatum* infection²² should help in this regard.

Liver—The liver is frequently enlarged. It was palpable in 39 of the 61 cases. It was not palpable in 12 instances, and in the remainder of the cases the status of the liver was not mentioned. In patients less than 1 year of age the liver has invariably been enlarged. In most instances its edge has been 2 to 3 fingerbreadths below the costal margin, but it may extend 7 fingerbreadths below the costal margin. The surface is usually firm and smooth to palpation, while the edge is frequently slightly rounded. Jaundice was present in cases 11 and 36. Ascites has occurred a few times.

Spleen—The spleen was palpable in 37 instances, not palpable in 14 cases and not mentioned in the remainder. It was palpable in all patients under the age of 1 year. It may be sufficiently enlarged to be felt below the level of the umbilicus, but the enlargement was more commonly measured in a few fingerbreadths. The surface usually felt moderately firm and was smooth. In all but 11 cases, when either the spleen or the liver was palpable the other organ was also palpable.

Gastrointestinal Tract—The symptoms relating to this tract are many and varied. Diarrhea was present in 12 cases, and in case 43 the symptom complex was indicative of an ulcerative enteritis. Vomiting was present in 6 of the cases. Hemorrhage per rectum occurred in cases 33 and 37. In 1 of these (case 37) it was massive and recurrent, but since an autopsy was not done the exact relationship of the hemorrhages to histoplasmosis is not known. Anorexia has been present in most of the cases, and loss of weight or true emaciation was almost always present.

Heart—On the basis of heart murmurs and irregular fever, subacute bacterial endocarditis was diagnosed in case 63. A vegetative endocarditis caused by *Histoplasma capsulatum* was found at autopsy.

Blood Pressure—A great majority of the patients showed no abnormality of the blood pressure. However in 3 cases a striking hypotension has been recorded (case 43, 80 systolic and 65 diastolic, case 50, 95 systolic and 55 diastolic, case 53, 88 systolic and 62 diastolic). At autopsy it was found that in each of these cases there was extensive caseation necrosis of the adrenals. Caseation necrosis was found in several other cases, as will be mentioned later, but the blood pressures recorded for these were not abnormally low.

Red Blood Cell Count—The red blood cell count was recorded in 38 cases. For the purpose of condensation of the data we have taken the average figure or the only figure that is given as a basis for the following statements. In only 2 cases was the count greater than 5,000,000. In 15 cases the count was between 4,000,000 and 5,000,000, in 19 cases between 3,000,000 and 4,000,000 and in 9 cases between 2,000,000 and 3,000,000, in 1 case the only count recorded was 1,500,000. It is evident that a moderate anemia is the rule in this disease and a severe anemia occurs fairly frequently.

Hemoglobin—The hemoglobin is reduced in proportion to the reduction in the number of red blood cells. In each case in which the blood was completely studied, the anemia was described as a hypochromic anemia, either of microcytic or of normocytic type.

White Blood Cell Count—In the table we have recorded the only count or the highest and the lowest count when more than one count was available. The total white cell count was recorded in 48 of the 71 cases. A count in the normal range, of 5,000 to 10,000, was recorded in 23 cases, but in 11 of these at least 1 other count was less than 5,000, and in 1 case above 10,000. Counts of 5,000 or less were recorded in 28 cases, and in 18 of these cases the counts were consistently below 5,000. Counts of over 10,000 were recorded in 15 cases, and in at least 2 of these cases (cases 4 and 20), histoplasmosis was associated with leukemia. In 1 of the 15 there was an accompanying count that fell into the leukopenic range, and in another case, a count that fell into the normal range. Restating these figures in another way, counts consistently in the leukopenic range were recorded in 18 cases, consistently in the normal range in 11 cases and consistently above 10,000 in 9 cases (disregarding the 2 cases of leukemia).

Differential White Blood Cell Count—This shows no consistent changes and is subject to wide variations. The neutrophilic granulocytes

22 (a) Van Perno, P. A., Benson, M. E., and Holinger, P. H. Specific Cutaneous Reactions with Histoplasmosis. Preliminary Report of Another Case, *J. A. M. A.* 117:436 (Aug 9) 1941. (b) Zarafonitis and Lindberg.¹⁸

ranged from 98 to 91 per cent, with 45 to 80 per cent most frequent. The lymphocytes ranged from 8 to 80 per cent, the common range being 20 to 60 per cent. The monocytes ranged from 0 to 16 per cent (from 1 to 4 per cent in most cases). In a few instances there was a considerable increase in the percentage of monocytes during the last few days or weeks before death. The percentage of eosinophilic granulocytes ranged from 0 to 32 per cent, 0 to 1 per cent being usual. From 0 to 11 per cent of basophilic granulocytes have been seen, but in the majority of instances no basophils were recorded.

Blood Smears—As has been pointed out, histoplasmosis was first diagnosed in life (case 11) by finding the yeastlike form of the fungus in the circulating monocytes. Since then blood smears have been studied intensively in known cases of the disease, but the organisms have been found in the monocytes in only 2 other cases (cases 25 and 32), and then only late in the course of the infection. In case 32 there was parasitization of both monocytes and neutrophils. In 1 of our cases (case 47), numerous *Histoplasma capsulatum* organisms were present in the cytoplasm of the neutrophilic granulocytes (fig 4) in smears taken on the last two days of life. Careful examination of daily smears taken earlier revealed no organisms, and at no time were organisms found in monocytes. The results of examination of blood smears for *Histoplasma capsulatum* can be considered diagnostically significant only when the organisms are found, and both the polymorphonuclear cells and the monocytes must be searched for them.

Temperature—The temperature is irregularly elevated to a variable degree in most cases of histoplasmosis. Most commonly it reaches 100 to 102 F at some time during the day, but temperatures as high as 107 F have been recorded. In only 2 instances in this series was the temperature reported as normal. Chills occurred in some cases, and in case 67 they recurred nightly. Night sweats were mentioned among the symptoms in some cases (cases 32 and 53).

Blood Proteins—Determinations of the blood proteins have been recorded in only 7 cases of histoplasmosis, but in each of these a definite abnormality has been demonstrated. In 4 of the cases reviewed the total protein content was normal but there was a reversal of the albumin-globulin ratio. In case 21, the albumin ranged from 2.6 to 3.1 and the globulin from 4.6 to 5.2 Gm per hundred cubic centimeters. The albumin was 2.9 and the globulin was 3.7 Gm per hundred cubic centimeters in case 24. In

case 53 the albumin was 3.9 and the globulin 4.3 Gm. In case 70 there was an albumin content of 2.5 Gm and a globulin content of 4.3 Gm. In the 3 others (cases 11, 32 and 51), a reduction of the total protein to 4.3, 4.7 and 4.4 Gm, respectively, was noted. Edema was described in case 11. Albumin was present in the urine in each of the cases in which there was a disturbance of the blood proteins.

Urine—Examination of the data on the collected cases does not reveal any specific changes in the urine. Albumin was present in 24 of the cases in which the urine was mentioned. Casts, red blood cells and white blood cells were also present in a smaller number of cases. It seems possible that *Histoplasma capsulatum* might be cultured from the urine of patients in some instances. It has been cultured from the urine of guinea pigs that had been infected by intravenous injection of the fungus by Reid and co-workers²¹.

Duration of the Disease—Infection with *Histoplasma capsulatum*, as far as we know now, is almost universally fatal, death occurring a few weeks or months and rarely some years after the infection. In the great majority of instances the infection lasted less than one year. For the 39 cases in this category, death occurred an average of five months after the onset of illness. In another group of 6 cases, symptoms lasted from one to two years, with an average of twenty-one months. In a third group there were 4 cases which lasted four, eight, ten and sixteen years. In case 5 the patient may have had histoplasmosis for many years but the history is indefinite. The third group contains the 3 cases in which *Histoplasma capsulatum* has produced longstanding chronic papular and ulcerative lesions of the skin. The average duration of symptoms in the 10 infants less than 1 year of age was five and one-tenth months, approximately the same as for the larger group of 39 patients which included these infants. Four patients (cases 17, 26, 57 and 59) are still living six, five two and two years after the diagnosis was established. Three of these (cases 17, 57 and 59) have had ulcerative lesions on the tongue as the only presenting sign of histoplasmosis.

METHODS OF DIAGNOSIS

Blood Smears—It has already been mentioned that the yeastlike form of *Histoplasma capsulatum* parasitizes the monocytes and the polymorphonuclear cells of the circulating blood. Examination of blood smears is the simplest and most readily available diagnostic procedure that

can be used. However, since in this large group of cases the organisms were found by examination of the blood cells in only 4 instances, it is obvious that the method should be relied on only when the organisms are found.

Sternal Bone Marrow—The sternal bone marrow has been studied by sternal puncture in at least 9 cases, the organism being found in 5 of these. Three of the cases in which this method of diagnosis was successful were cases of histoplasmosis in infants. In case 54 *Histoplasma capsulatum* was successfully cultured from material obtained by sternal puncture.

Biopsy—In 29 of the cases in this series, it has been possible to establish a diagnosis by histologic examination of biopsy material. In 3 of these cases the material for biopsy was obtained by a sternal puncture. In 2 cases sternal marrow and other biopsies were both diagnostic. In some instances (e.g. cases 37 and 53), the diagnosis was confirmed by culture of some of the material obtained for biopsy. Up to the present time, biopsy appears to be the most successful method of detecting this disease.

Cultures—The only means for establishing a positive diagnosis of histoplasmosis at the present time is to obtain a culture of the organism and identify it by means of its definitive characteristics in the mycelial form. The mycelial form develops on nearly all of the ordinary bacterial and fungous mediums when they are kept at room temperatures. On fungous mediums, such as Sabouraud's, the mycelial form will develop at incubator temperatures, but growth is less rapid than at room temperatures. The yeastlike form, as obtained directly from the tissues or the blood, can be grown at 37 C on blood agar and other neutral or slightly basic mediums which have a high content of protein. The tubes may or may not be sealed. The organism grows slowly and may therefore be difficult to isolate from contaminants. The cultures should be kept for at least two and better for three weeks before they are discarded as negative.

At present there appears to be only one species *Histoplasma capsulatum*, of the genus *Histoplasma*. The most recent and the best discussion of the classification of this fungus was published in 1941 by Conant.¹³

Cultures of *Histoplasma capsulatum* have been obtained in 23 of the cases in this series. This number would undoubtedly have been much higher if the culture mediums in other cases had not been discarded after a lapse of only four or five days. In 18 instances *Histoplasma capsulatum* was grown from the tissue obtained for biopsy or at autopsy. In 9 instances the organism

was grown in cultures of the blood, and in 1 instance it was grown from a culture of sternal marrow. In case 39 it was cultured from sputum. In several of the cases it was obtained from more than one source.

Cutaneous Test—Another method of diagnosis which holds some promise of being useful is a cutaneous test. The intradermal injection of a filtrate obtained from the liquid medium in which the fungus has grown results in the production of erythema and a wheal at the site of injection in infected persons. Such a test was developed and used successfully in a patient having histoplasmosis by Van Pernis, Benson and Hollinger.^{22a} The same sort of test was developed by Zarafonitis and Lindberg,¹⁸ and it was found to give excellent reactions in rabbits infected with *Histoplasma capsulatum*. The antigen used in case 71 yielded negative results. This antigen was ten months old and may have been inactive.

Inoculation of Animals—Many laboratory animals have been found susceptible to infection with *Histoplasma capsulatum*, among them mice,²² guinea pigs,^{23a} rats,⁹ rabbits,²⁴ dogs,² monkeys⁸ and chick embryos.²⁶ It seems probable that in some instances in which it is impossible to obtain uncontaminated material for culture, the subcutaneous, intraperitoneal or intravenous injection of ground biopsy material into one or more of these animals might render the isolation of *Histoplasma capsulatum* simpler than the use of culture mediums alone. In case 53, lymph nodes were removed for culture and isolation of the organism on two separate occasions. We succeeded in obtaining the organism in culture each time, but we also successfully inoculated young mice with suspensions of the nodes. The mice were inoculated intravenously, and all became infected with the organism.¹² Injection of biopsy material from case 71 into guinea pigs failed to induce an infection. Intraperitoneal injections into mice are known to be satisfactory.^{22a}

TREATMENT

Many types of treatment for histoplasmosis have been tried during the last ten years. Some have met with questionable success, but most

23 De Monbreun,⁸ Parsons,¹² Tager and Liebow.¹⁷
23a Negroni,^{14a} Redaelli and Ciferri.^{14b} Reid and others.²¹

24 Redaelli and Ciferri.^{14b} Zarafonitis and Lindberg.¹⁸ Van Pernis and others.^{22a}

25 De Monbreun,⁸ De Monbreun, W. A. The Dog as a Natural Host of *Histoplasma Capsulatum*. Case of Histoplasmosis in This Animal, *Am J Trop Med* 19 565 (Nov) 1939.

26 Moore, M. *Histoplasma Capsulatum*. Its Cultivation on the Chorioallantoic Membrane of the Developing Chick and Resultant Lesions, *Am J Trop Med* 21 627 (Sept) 1941.

have not appeared to alter the course of the disease. In case 26, biopsy of a lymph node resulted in a diagnosis of leishmaniasis. On the basis of this diagnosis, neostam,²⁷ an antimony preparation, was given with resulting clinical recovery. Meanwhile sections of the lymph node were reexamined and the proper diagnosis of histoplasmosis was made. At the time of the last report,²⁸ October 1942, this patient was in good health and working every day, four years after his treatment. On the basis of this result we gave neostam (stibamine glucoside) in case 53. Because of the toxic effect of the drug it had to be discontinued when only 0.56 Gm. had been administered. At about the same time neostam was given in case 50, but it was soon refused by the patient. In case 57 the patient has shown striking improvement following treatment, first with an antimony preparation and then with antimony alternated with one of the new diamidine preparations.²⁹ This patient is still alive. The patient in case 69 was treated much as was the one in case 57. The diamidine preparation was stilbamidine^{29a} (4,4-diamidinostilbene), and the antimony was in the form of neostibosan.³⁰ Treatment was unsuccessful.

Case 50 is of special interest. As mentioned in the preceding paragraph, an antimony preparation was used first. Only a small amount of the substance was administered. The patient was then given 4 Gm. of sulfathiazole per day. He continued to feel worse, hence this was discontinued after ten days. In addition to these medications, potassium permanganate soaks, gentian violet, 2 per cent thymol in olive oil and sulfanilimide dusting powder all failed to induce healing of the superficial lesions. In this case the diagnosis had been established by biopsy and successful cultural studies of material removed from the lip and the perianal region. At autopsy, lesions comparable to those of histoplasmosis were found in many organs and the adrenals were the site of caseation necrosis. The tissues were carefully examined by Dr. A. L. Amolsch, who is thoroughly familiar with histoplasmosis. He could not find organisms in the tissues after death, although he did find small clear areas of the size and shape of the capsule of *Histoplasma capsulatum*. It is possible that the infection had been cured by neostam or sulfathiazole and that the patient died of adrenal insufficiency.

27 Neostam (stibamine glucoside) was obtained from Burtoughs-Wellcome & Co., Inc., New York city.

28 Mantel, cited by Melenev.^{19a} Tompkins, R. D. Personal communication to the authors.

29 Melenev, H. E. Personal communication to the authors.

29a Stilbamidine (4,4-diamidinostilbene) was obtained from Merck & Co., Inc., Rahway, N. J.

30 Neostibosan (Bayer) is a pentavalent antimony compound, diethylamine paraaminophenylstibinate.

Among other substances that have been used in treatment are blood transfusions, potassium arsenite, neoarsphenamine, sulfarsphenamine, acetarsone, sulfanilimide, sulfadiazine, sodium thiosulfate, iodides, ionized metals, thymol, bone marrow, pentnucleotide, autogenous vaccines, ammonium and potassium tartrate, stibophen, quinine, and quinacrine hydrochloride. In general, their use has not altered the course of the disease. However, it should be emphasized that in many instances only small amounts of the substances were administered and these late in the course of the disease. Ultraviolet irradiation has been used unsuccessfully on the superficial lesions.

Roentgen rays and radium have been used with results that seem equivocal. After a diagnosis of carcinoma of the tongue by biopsy in case 17, treatment with radium resulted in healing. The ulcer of the tongue recurred one year later and was treated with "superficial x-rays." Biopsy of this recurrent lesion showed *Histoplasma capsulatum* in the tissues. The ulcer healed, and the patient has shown no evidence of histoplasmosis for the past five years. In case 47, roentgen irradiation was used in the treatment of enlarged lymph nodes that were thought to be the site of lymphosarcoma. The nodes were much reduced in size. A later course of irradiation, also based on a supposition of lymphosarcoma, was given. As stated in the case report, lymphosarcoma was not found at autopsy, and since widely disseminated lesions of histoplasmosis were found, it can be said that we were treating histoplasmosis. It is our opinion that the second course of roentgen irradiation was deleterious. In case 71 roentgen therapy in fractionated doses was applied to large, exquisitely tender ulcers of the lip and tongue as well as over the region of ulcerated lesions in the pharynx. Nine hundred roentgens was given at each of several points. During and following this treatment, tenderness of the ulcers of the tongue and lip disappeared and the lesions showed some reduction in size. Healing never occurred. The pharyngeal and laryngeal lesions showed no evidence of improvement following the treatment. Roentgen therapy has been used in several other cases without success.

Amputation was performed in a case of histoplasmosis of the knee (case 58), but the patient died nine days after the operation, so appraisal of this form of treatment is not possible.

OBSERVATIONS AT AUTOPSY

Autopsies were performed in 56 of the cases collected in this review. Since in several we had only fragmentary knowledge of the observations made, all of the figures given here are undoubtedly

low They will be cited, nonetheless, since they indicate the relative liability of the various organs to involvement In the table we have identified as instances of generalized histoplasmosis those cases in which the author stated that the involvement of the organs was generalized, and also those cases in which both the liver and the spleen as well as some other organ were involved When the description of the case has stated that certain specific organs were involved, we have included the more important of these in the table

It can be noted that 40 of the cases are listed as instances of generalized involvement Specific mention of involvement of lymph nodes was found in 37 instances, while the lungs showed the lesions of histoplasmosis in at least 34 Of the remaining organs the adrenals were most frequently involved, lesions in them being mentioned 18 times Caseation necrosis, which closely resembles that seen in tuberculosis, occurred in 11 cases (cases 10, 24, 28, 40, 43, 50, 52, 53, 60, 69 and 70) Lesions of the gastrointestinal tract occurred with moderate frequency and were found in all of the subdivisions of the tract Such lesions were mentioned in 15 cases in this series, the lesions being found in the ileum or the colon most frequently In many instances they took the form of large craterous ulcers, as in cases 2, 8, 43, 44 and 53 At other times, occasional foci of parasitized cells were found in the mucosa of the stomach and appendix, as in case 47 Lesions of the bone marrow were found in 16 instances The kidneys were frequently involved, foci of infection being mentioned in 11 cases In some cases small granulomatous areas were found in the interstitial tissue, while in others reticuloendothelial cells in the glomerular tufts were parasitized Various lesions of the skin were described in 10 cases, but in several of these the direct connection between the infection with *Histoplasma capsulatum* and the lesions was not made clear

As indicated previously, ulcerative lesions of the oral cavity are common Lesions in the mouth were noted in 9 autopsies, and diagnosis of such lesions in 6 additional cases by biopsy has been made The oral lesions in case 37 undoubtedly belong in this class, but they were not examined by biopsy Lesions in the nose have been identified by biopsy or at autopsy in 6 cases Histoplasmosis of the larynx has occurred at least 8 times In 2 of these cases (cases 57 and 71) the initial lesion of the disease was on the tongue Lesions have been found in the pancreas 6 times and in the thymus 4 times

A vegetative endocarditis has been described in 3 cases In case 63 the mitral and aortic

valves were involved The aortic valve was involved in case 21, while in case 71 the tricuspid valve was involved In each of these cases *Histoplasma capsulatum* was found in the vegetations A verrucous endocarditis of the tricuspid and aortic valves was found in case 4, but there is no statement as to its cause in the case report

Lesions were found in the ear and brain in case 11, in the brain in case 21, in the parathyroids in case 53, in the prostate in case 23, in the trachea in cases 15 and 62 and in the knee joint and femur in case 58

Miliary lesions resembling miliary tubercles have been found in at least 12 of the cases reviewed (cases 2, 22, 24, 34, 40, 47, 52, 53, 67, 69, 70 and 71) In cases 24, 34 and 70, active tuberculosis was also present, and it may have been the cause of the miliary lesions

COMMENT

A review of the 56 cases of histoplasmosis which have been mentioned or described in the literature and of 15 cases which at the time of this review have not yet been published reveals a disease of worldwide distribution Cases of the disease have appeared in 20 states and in the District of Columbia and in 10 countries outside the United States The disease has been recognized in the United States at least 56 times, and 31, or more than half, of the cases have occurred in states lying along the Mississippi River and its main tributaries Michigan is the only state in which a large number of cases of the disease have been recognized which does not fall into this group If the cases observed there are added to the group, they bring to 41 the number of cases from the central area of the United States We are unable to attribute definite significance to these facts or to the fact that no cases have been reported from the New England states

Histoplasmosis has occurred in 51 white persons, 7 Negroes and 2 mulattoes The number of cases of its occurrence in Negroes appears to be high in proportion to its incidence in white persons This may indicate greater susceptibility on the part of the Negro However, a large proportion of the cases in the United States has come from states having a relatively high Negro population This and the occupations of the Negro are factors which must be considered carefully in this connection before a judgment is made

A study of the sex incidence of histoplasmosis yields interesting results We find that males and females are affected alike before the tenth year of life In persons over 10 years, the disease

has occurred 7 times in males for every time it has been recognized in a female. A type of occupation involving exposure to the fungus in nature may be the determining factor. The effect of the gonads on susceptibility may be important, and it is interesting to note that of the 6 female patients older than 10 years of age, only 2 were less than 50. In other fungous diseases, such as actinomycosis, coccidiosis and sporotrichosis, infection of males is also more frequent.³¹

Histoplasmosis has occurred during the first year of life in 11 cases as frequently as it has occurred during any later decade. After the end of the first year the number of cases per decade is very low but shows gradual and progressive increases to reach a plateau in the fifth, sixth and seventh decades. In case 66, the fact that buccal ulcerations developed at the time that the child was weaned suggests that infection with the fungus was coincident with the start of bottle feeding. In 3 cases the disease manifested itself during the second month of life. This indicates that the fungus is most probably harbored by some member of the family or is closely associated with the environment in which the child lives. Up to the present, congenital infection with *Histoplasma capsulatum*, such as occurs with toxoplasma infection,³² has not been evident in any case. In the future the use of the intradermal test²² on the members of the family might help in studying the epidemiology of the disease. De-Monbreun,²⁵ Thuringer,^{33a} Callahan,^{33b} and Parsons and Everett^{33c} found dogs naturally infected with *Histoplasma capsulatum*.

The occupations of 30 patients over 12 years of age were stated in the data available for the table. Ten of these were farmers, 4 were laborers, 2 were bartenders and 2 were waiters. The occupations of the remainder do not appear to be related, and it is felt that no definite conclusions can be drawn from these figures. It must be remembered that up to the present time the fungus has not been found in its vegetative form in nature.

The signs and symptoms of histoplasmosis show wide variation. They occurred (considering only the cases in which each sign or symptom

was mentioned) as follows: Irregular, low or moderate fever was present in 47 of 49 cases, moderate to severe anemia of the hypochromic type, in 44 of 46 cases, palpable liver, in 39 of 51 cases, palpable spleen, in 37 of 51 cases, enlarged lymph nodes, in 29 of the 42 cases in which they were mentioned, leukopenia, in 28 of 48 cases, albuminuria, in 24 of 37 cases. Lesions of the lungs have been noted in 34 of the 61 cases analyzed, symptoms referable to the gastrointestinal tract, in 28 of the 61. Twenty-six of the 61 patients have shown loss of weight, and in 19 of these emaciation was described. Ulcerative lesions of the oropharynx were present in 21 of the 61, ulcerations of the skin, in 9, papular lesions, in 4, and lesions of the larynx, in 10. In case 32, external examination of the fundus of the eye showed lesions which were thought to be caused by *Histoplasma capsulatum*. In each of the 7 cases in which the values for blood proteins have been recorded they have been abnormal: low total protein in 3 cases and reversal of the albumin-globulin ration in 4.

Histoplasmosis may be a disease of long or of short duration. In more than four fifths of the cases the duration of symptoms averaged five months. In 3 cases, in all of which chronic ulcerative lesions of the skin were present, the infection appeared to have lasted for eight, ten and sixteen years before ending fatally. The patients of cases 17, 26, 57 and 59 are still living after intervals of two to six years. In 3 of these (cases 17, 57 and 59) ulceration of the tongue was the only demonstrable site of infection.

In attempting differential diagnosis one should remember that histoplasmosis mimics many more common diseases. It produces miliary lesions, ulcerations of the intestinal tract and caseation necrosis which resemble closely the same lesions produced by tuberculosis. It causes enlargement of the spleen, liver and lymph nodes such as one sees in leukemia and in Hodgkin's disease. In case 49 histoplasmosis and Hodgkin's disease occurred together. It has been confused with Banti's disease and atrophic cirrhosis. It produces ulcerative lesions of the oropharynx and larynx, and in several instances (cases 17, 53, 56 and 59) the clinical diagnosis before biopsy was carcinoma. In 3 cases *Histoplasma capsulatum* has been the cause of a vegetative endocarditis. The leukopenia and anemia must be differentiated as to causation from aleukemic leukemia and other blood dyscrasias. In cases of extreme hypotension, histoplasmosis must be thought of as a possible cause of adrenal insufficiency. Some

31 Jacobson, H. P. *Fungous Diseases. A Clinico-Mycological Text*, Springfield, Ill., Charles C Thomas, Publisher, 1932.

32 Sabin, A. B. Toxoplasma Neutralizing Antibody in Human Beings and Morbid Conditions Associated with It, *Proc Soc Exper Biol & Med* **51**: 6 (Oct.) 1942.

33 (a) Thuringer, J. M. Histoplasmosis. Report of Its Occurrence in a Dog, *Arch Path* **37**: 140 (Feb.) 1944. (b) Callahan, W. P., Jr. Spontaneous Histoplasmosis Occurring in a Dog, *Am J Trop Med* **24**: 363 (Nov.) 1944. (c) Parsons, R. J., and Everett, M. Histoplasmosis in a Dog. Report of a Case, to be published.

features of histoplasmosis very closely resemble the leishmanian infections, kala azar, cutaneous leishmaniasis and espundia. Smears, biopsies and cultures, done by persons acquainted with both infections, will be required for differentiation.

In the present series of cases, biopsy has been the most successful method of diagnosis during life. Biopsy with culture of the organism has been successful in many instances. Examination of the sternal bone marrow has shown the organisms in 5 cases and failed to show them in 4. Since the organisms have been found in blood smears in only 4 cases, this type of examination cannot be relied on for diagnosis. Invasion of the blood cells by sufficient numbers of organisms to be found readily in blood smears appears to occur late in the disease. Culture of the blood has yielded positive results in 9 instances. Examination by smear and by culture of the buffy coat of centrifuged blood might increase the ability to establish the diagnosis during life. Meleney^{19a} has suggested that monocytes which are heavily parasitized might be heavier than the other cells and therefore might accumulate at the bottom of the centrifuge tube. Smear and culture of the sediment might prove diagnostic. In case 39 *Histoplasma capsulatum* was cultured from the sputum of a patient supposed to have tuberculosis. Cultural studies of the stools have been suggested by Cummie and Kessel^{11a} and by Henderson, Pinkerton and Moore,³⁴ in the belief that with extensive intestinal ulcerations *Histoplasma capsulatum* is probably present in the feces.

Histoplasmosis is a unique fungous disease. The yeastlike form of the fungus characteristically attacks or is attacked by the cells of the large macrophage, or reticuloendothelial, system. Since cells of this group are normally present in every tissue of the body (with the exception of cartilage and the cortex of bone), it is not surprising to find that parasitized macrophages may be found in any tissue. In the liver, the Kupffer cells are most frequently parasitized, and they undergo hypertrophy and hyperplasia. In some cases, e. g. case 53, a granulomatous process developed in the portal areas. In most of the other organs single macrophages may be found parasitized, or large numbers of them may be found forming one of the components of a granulomatous lesion. When the fungus induces a lesion on a surface, an

ulcer with a granulomatous base is produced. When the lesion is within a tissue or organ, granulomas occur, which in some cases resemble miliary tubercles. The centers of the granulomatous lesions may undergo caseation necrosis. In the adrenals this process has been so advanced in several cases that death appears to have resulted from adrenal insufficiency.

SUMMARY

A review of 71 cases of histoplasmosis reveals a fungous disease which is being found with increased frequency, particularly in the United States of America. Up to the present time, the disease has proved fatal in most instances.

The most common signs and symptoms, in the order of their decreasing frequency are fever, hypochromic anemia, hepatomegaly, splenomegaly and lymphadenopathy. Anorexia and loss of weight are common. Ulceration of the oral mucosa (particularly the tongue), various types of cutaneous lesions and ulceration of the pharynx and larynx occur frequently. Other manifestations occur occasionally.

The yeastlike, or parasitic, form of the fungus characteristically is found in cells of the large macrophage, or reticuloendothelial, system. At autopsy, the organs are found to be involved in the following order in respect to frequency: spleen, liver, visceral lymph nodes, lungs, bone marrow, oral mucosa, adrenals, gastrointestinal tract, peripheral lymph nodes, kidneys and larynx. Vegetative endocarditis has occurred 3 times. Any or all of the remaining organs may be involved.

The disease affects persons of all ages. However, it has occurred in as many cases during the first year of life as in any later decade. The first, fifth, sixth and seventh decades of life have shown the greatest incidence of the disease. The sexes are equally affected up to and including the tenth year of life. After the tenth year, 7 out of 8 patients have been male.

The portal of entry of the fungus is still not known. More and more the evidence accumulating indicates that the mouth is the most frequent site of entrance. The large number of patients who have ulcerated lesions of the mouth, pharynx and gastrointestinal tract points to this conclusion. The many cases in which lesions of the nose, pharynx, larynx and lungs are present may be assembled as evidence that the respiratory tract is also a portal of entry. Another, and smaller, group of cases suggests entrance through the skin. The fungus is unknown in its vegetative form in nature, but the parasitic form has been identified in the dog.³³ What appears to be

34 Henderson, R. G., Pinkerton, H., and Moore, L. T. *Histoplasma Capsulatum* as a Cause of Chronic Ulcerative Enteritis, *J. A. M. A.* 118: 885 (March 14) 1942.

the same organism has also been found in mice,³⁵ rats³⁶ and ferrets³⁷

Treatment of histoplasmosis is still in an experimental state. Certain antimony preparations and a new diamidine preparation (see section on treatment) appear to hold promise for the future.

Diseases which must be differentiated most frequently from histoplasmosis are tuberculosis, Hodgkin's disease, aleukemic leukemia and malignant neoplasms.

Successful antemortem diagnosis has most frequently been provided by histologic examination of biopsy material. Blood cultures, cultures

of biopsy material and smears or scrapings from superficial lesions have been successful in several instances. Least successful of the laboratory methods used, although with a few outstanding exceptions, have been the examination of blood smears and that of sternal marrow. This statement should not cause the abandonment of these two methods, as they are simple and when successful are of great value.

NOTE—Several papers³⁸ have come to our attention since this review was submitted for publication. Each contains the description of a case of histoplasmosis which has not been included in the present review.

35 Shortt, H. E. The Pathogenicity of Insect Flagellates to Vertebrates, with Special Reference to *Herpetomonas Ctenocephali*, Fantham, Indian J. M. Research **10** 908 (April) 1923.

36 Sangiorgi, G. Blastomycosis spontanea nei Muridi, *Pathologica* **14** 493 (Aug.) 1922.

37 Levine, N. D., Dunlap, G. L., and Graham, R. An Intracellular Parasite Encountered in Ferret, *Cornell Vet* **28** 249 (July) 1938.

38 Boltjes, B. Histoplasmosis. Report of a Case with Brief Review of the Literature, *J. Kansas M. Soc.* **44** 226 (July) 1943. Moore, M., and Jorstad, L. H. Histoplasmosis and Its Importance to Otorhinolaryngologists. A Review with Report of a New Case, *Ann. Otol., Rhin. & Laryng.* **52** 779 (Dec.) 1943. Schlumberger, H. G., and Service, A. C. A Case of Histoplasmosis in an Infant with Autopsy, *Am. J. M. Sc.* **207** 230 (Feb.) 1944.

RESPIRATION AND CIRCULATION IN PATIENTS WITH OBSTRUCTION OF THE SUPERIOR VENA CAVA

CEREBRAL FACTORS IN DYSPNEA AND ORTHOPNEA

M D ALTSCHULE, M D

BOSTON

A IGLAUER, M D

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The signs of obstruction of the superior vena cava have aroused clinical interest since Stokes¹ described the syndrome over a century ago. The recent reviews of Ehrlich and others,² Ochsner and Dixon³ and Hinshaw and Rutledge⁴ discussed in detail the anatomic and clinical manifestations of this disorder. A number of authors⁵ have described the findings on angiocardiology. The abnormal physical findings consist of striking venous engorgement, cyanosis and often edema which are limited to the head, neck, arms and chest. Common complaints are headache, dizziness, fulness in the head, mental clouding and respiratory manifestations such as dyspnea, orthopnea and periodic breathing; in addition, paroxysmal dyspnea has been described by several authors,⁶ and Ferris⁷ reported "brief

but severe attacks of hyperpnea" in 1 patient. The occurrence of respiratory symptoms in patients with stasis and with high venous pressure limited to the superior vena cava and its tributaries and with no congestion of the lungs affords an opportunity for study of factors important in the genesis of dyspnea and of orthopnea.

MATERIALS AND METHODS

Five male patients for whom a diagnosis of obstruction of the superior vena cava was made and who showed dyspnea, orthopnea or periodic breathing were studied; the periodic breathing was only moderately severe, no periods of apnea occurring. The patients ranged in age from 20 to 64 years. The diagnoses were as follows: mediastinal lymphoma (patients 1 and 3), mediastinal Hodgkin's disease (patient 2), metastatic carcinoma (patient 4) and syphilitic aneurysm of the aorta (patient 5). Additional studies were made of 3 of these patients after improvement occurred, 2 (patients 1 and 2) were studied when all manifestations of obstruction of the superior vena cava had disappeared after roentgen irradiation of the chest and the third (patient 3) after the symptoms had regressed spontaneously, only slight changes in the abnormal physical signs having taken place.

Studies of the respiratory dynamics were made with a Tissot spirometer or with a Benedict-Roth apparatus, with the patient sitting in bed. Venous pressure was measured by the method of Moritz and von Tabora,⁸ the arm to

730, 1935. (c) Erganian, J., and Wade, L. J. Chronic Fibrous Mediastinitis with Obstruction of the Superior Vena Cava, *J Thoracic Surg* 12: 275, 1943.

7 Ferris, E. B., Jr. The Effect of High Intracranial Venous Pressure upon the Cerebral Circulation and Its Relation to Cerebral Symptoms, *J Clin Investigation* 18: 19, 1939.

8 Moritz, F., and von Tabora, D. Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch f klin Med* 98: 475, 1910.

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1 Stokes, W. A Treatise on the Diagnosis and Treatment of Diseases of the Chest. I Diseases of the Lung and Windpipe, Dublin, Hodges and Smith, 1837, p 231.

2 Ehrlich, W., Ballou, H. C., and Graham, E. A. Superior Caval Obstruction with a Consideration of the Possible Relief of Symptoms by Mediastinal Decompression, *J Thoracic Surg* 3: 352, 1934.

3 Ochsner, A., and Dixon, J. L. Superior Vena Caval Obstruction. Review of the Literature and Report of Cases of Traumatic and Infectious Origin, *J Thoracic Surg* 5: 641, 1936.

4 Hinshaw, H. C., and Rutledge, D. I. Lesions in the Superior Mediastinum Which Interfere with Venous Circulation, *J Lab & Clin Med* 27: 908, 1942.

5 (a) Taylor, H. K., and McGovern, T. Evaluation of Angiocardiography, *J A M A* 121: 1270 (April 17) 1943. (b) Steinberg, I., and Robb, G. P. Mediastinal and Hilar Angiography in Pulmonary Disease. A Preliminary Report, *Am Rev Tuberc* 38: 557, 1938.

6 (a) Arrillaga, F. C., and Taquini, A. C. Fisiopatogenia de la cianosis en los tumores del mediastino, *Arch urug de med, cir y especialid* 5: 305, 1934. (b) Lian, C., and Abaza, A. La dissociation de la pression veineuse et de la vitesse circulatoire, signe caracteristique de l'obstruction de la veine cave superieure, *Bull et mém Soc med d hôp de Paris* 51

tongue time with sodium dehydrocholate,⁹ the arm to lung time with ether¹⁰ and the lung to brain time with carbon dioxide¹¹, all of these studies were done with the patient recumbent. Measurements of cardiac output were made by the method of Starr and Gamble¹² with the patient sitting in bed. Studies of the blood gases were made by the method of Van Slyke and Neill¹³.

OBSERVATIONS

The respiratory dynamics were studied in 4 patients. When respiratory manifestations were present the average respiratory rate ranged be-

tween 19 and 35 with an average for all of 24 per minute (table 1). After the disappearance of respiratory symptoms in 3 patients the rate was 14 to 16 per minute. The respiratory volume per minute when first studied ranged between 772 and 1333 liters, with an average of 999 liters. After improvement had occurred in 3 patients the values were 586 to 720 liters per minute. The volume of tidal air was within the normal range, measuring 380 to 450 cc. when respiratory symptoms were present and 420 to 480 cc. after improvement had occurred.

The amount of carbon dioxide in the alveolar air ranged between 4.01 and 5.1 per cent, with

TABLE 1—*Studies of Respiratory Dynamics*

Patient	Respirations per Min	Tidal Air, Cc	Respiratory Volume, L/min	Alveolar Air Carbon Dioxide, per Cent	Arterial Blood Oxygen Saturation, per Cent	Vital Capacity, Cc	Comments
1	19	405	772	5.10	93	2,500	Orthopnea
	14	420	586	5.55	92	2,500	No orthopnea
2	19	440	835	4.53	9	1,210	orthopnea, periodic breathing
	14	480	672	5.21	91	1,650	No periodic breathing or orthopnea
3	23	450	1025	4.26	94	1,700	Periodic breathing
	16	450	720	5.18		1,700	No periodic breathing
4	35	380	1320	4.01		900	Dyspnea at rest orthopnea

TABLE 2—*Studies of Venous Pressure and Circulation Time*

Patient	Venous Pressure, Cc		Circulation Time—Seconds			Comments
	Antecubital	Femoral	Arm to Tongue (Sodium Dehydrocholate)	Arm to Lung (Ether)	Lung to Brain (Carbon Dioxide)	
1	27		23	17	10	Orthopnea
	8	8	17		9	No orthopnea
2	37		25		.	Periodic breathing, orthopnea
	4		17		.	No periodic breathing or orthopnea
3	29	8	23		8	Periodic breathing
	22		26			No periodic breathing
4	32	4	*			Dyspnea at rest orthopnea
5	23†	5	35‡			Dyspnea at rest orthopnea

* No end point

† Spinal fluid pressure was 337 mm

‡ The femoral vein to tongue time was 17 seconds

9 Winternitz, M., Deutsch, J., and Brull, Z. Eine klinischbrauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholinjektion, *Med. Klin.* 27:986, 1931

10 Hitzig, W. M. Measurement of Circulation Time from Antecubital Veins to Pulmonary Capillaries, *Proc. Soc. Exper. Biol. & Med.* 31:935, 1934

11 Gubner, R., Schnur, S., and Crawford, J. H. The Use of CO₂ Inhalation as a Test of Circulation Time, *J. Clin. Investigation* 18:395, 1939

12 Starr, I., Jr., and Gamble, J. C. An Improved Method for the Determination of Cardiac Output in Man by Means of Ethyl Iodide, *Am. J. Physiol.* 87:450, 1928

13 Van Slyke, D. D., and Neill, J. M. The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* 61:523, 1924

an average of 4.58 per cent when first studied and rose to 5.18 to 5.55 per cent after the disappearance of respiratory symptoms (table 1).

The oxygen saturation of the arterial blood was 92 to 94 per cent irrespective of the presence or absence of respiratory symptoms (table 1).

The vital capacity was low in all 4 patients ranging between 900 and 2500 cc. when first studied (table 1). After the disappearance of respiratory symptoms the vital capacity was unchanged in the 1 patient (no. 3) in whom improvement was spontaneous and increased slightly in the 2 (nos. 1 and 2) in whom improvement followed roentgen irradiation.

The pressure in the antecubital veins ranged from 23 to 27 cc of water when the patients showed respiratory symptoms, at this time the pressure in the femoral vein was 4 to 8 cm of water (table 2). When the respiratory symptoms of 2 patients (nos 1 and 2) disappeared after roentgen radiation, the antecubital venous pressure fell to normal. The patient in whom spontaneous regression of hyperventilation and periodic breathing occurred showed a fall in antecubital venous pressure of only 7 to 22 cm of water.

The circulation time between arm and tongue was prolonged, measuring twenty-five to thirty-five seconds when the patients had respiratory symptoms, the femoral to tongue time was normal (table 2). The arm to tongue time fell to the normal value of seventeen seconds in the 2 patients (nos 1 and 2) who improved after roentgen irradiation and showed no significant

is elevated,¹⁴ while that in the veins draining into the inferior cava is normal.¹⁵ The results of the present study corroborate these earlier observations. Burwell^{14m} found, in addition, that the pressure in the collateral veins over the chest is intermediate between that in the upper and that in the lower extremities. Only a few reports on the circulation time in this syndrome are available. In most of the cases studied slowing of the arm to tongue time was noted,¹⁶ although Hitzig^{14k} found it normal or only slightly slowed. The contention of Lian and Abaza^{6b} that the arm to tongue circulation time is always normal and that this "dissociation" between a high venous pressure and a normal circulation time is diagnostic of obstruction of the superior vena

TABLE 3—Studies of Cardiac Output and Blood Gases

Patient	Cardiac Output		Arteriovenous Oxygen Difference, Vol per Cent		Comments
	L/Min	L/100 Cc O ₂	Arm	Leg	
1	3.84	1.75	9.8	5.6	Orthopnea
	3.91	1.72	4.6		No orthopnea
2			8.5		Periodic breathing
			5.6		? orthopnea No periodic breathing or orthopnea
3	4.70	1.57	10.4	8.5	Periodic breathing
			6.9		No periodic breathing

change in the patient (no 3) who improved spontaneously. A single measurement of arm to lung time was abnormally prolonged when the arm to tongue time was slowed. The lung to brain time was not abnormal at any time.

The cardiac output of 2 patients (nos 1 and 3) was normal when respiratory symptoms were present, and that of 1 of them was normal after these symptoms had disappeared (table 3).

The local arteriovenous oxygen differences were calculated from measurements made on blood taken from the femoral artery and from the femoral and antecubital veins (table 3). When respiratory symptoms were present, the arteriovenous difference was increased in the upper extremities and was normal in the lower. There was a decrease in arteriovenous oxygen difference in the arms of all 3 patients studied after regression of respiratory symptoms.

COMMENT

A number of authors have studied venous pressure in patients with obstruction of the superior vena cava, and all are agreed that the pressure in the tributaries of the superior cava

14 (a) Ehrlich, Ballon, and Graham² (b) Ochsner and Dixon³ (c) Hinshaw and Rutledge⁴ (d) Lian and Abaza^{6b} (e) Erganian and Wade^{6c} (f) Ferris⁷ (g) Burger Ueber die klinische Bedeutung des Valsalvaschen Versuches, *Munchen med Wchnschr* 68 1066, 1921 (h) Kroetz, C Die Koeffizienten des klinisch messbaren Venendruckes, *Deutsches Arch f klin Med* 139 325, 1922 (i) Villaret, M, and Martiny, M Étude de la pression veineuse peripherique dans les syndromes mediastinaux. Son intérêt de controle pour le diagnostic et le pronostic, *Presse med* 37 249, 1929 (j) Villaret, M, and Desoille, H Exemples cliniques montrant l'intérêt general de la phlebopiezometrie au point de vue du diagnostic, du pronostic et de la therapeutique, *ibid* 40 1477, 1932 (k) Hitzig, W H The Use of Ether in Measuring the Circulation Time from the Antecubital Veins to the Pulmonary Capillaries, *Am Heart J* 10 1080, 1935 (l) Ferris, E B, Jr, and Wilkins, R W The Clinical Value of Comparative Measurements of the Pressure in the Femoral and Cubital Veins, *ibid* 13 431, 1937 (m) Burwell, C S A Comparison of the Pressures in Arm Veins and Femoral Veins with Special Reference to Changes During Pregnancy, *Ann Int Med* 11 1305, 1938 (n) Hussey, H H The Effect of Mediastinal Lesions on Pressures in the Antecubital and Femoral Veins, *Am Heart J* 17 57, 1939 (o) Rutledge, D I, and Gray, H K Indeterminate Type of Obstruction of the Superior Vena Cava, *Proc Staff Meet, Mayo Clin* 14 337, 1939 (p) Veal, J R, and Hussey, H H The Use of Exercise Tests in Connection with Venous Pressure Measurements for the Detection of Venous Obstruction in the Upper and Lower Extremities, *Am Heart J* 20 308, 1940 (q) Gray, H K, and Skinner, I C Constrictive Occlusion of the Superior Vena Cava, *Surg, Gynec & Obst* 72 923, 1941 (r) Eyster, J A E, and Middleton, W S Clinical Studies on Venous Pressure, *Arch Int Med* 34 228 (Aug) 1924 (s) Porot, M A Les fortes hypertensions cephalorachidiennes d'origine veineuse, *Rev neurol* 1 1173, 1930 (t) Smirk, F H Observations on the Causes of Oedema in Congestive Heart Failure, *Clin Sc* 2 317, 1936 (u) Wartman, W B A Study of the Venous Pressure in Some Common Diseases, *Am J M Sc* 190 464, 1935

15 Ochsner and Dixon³ Hinshaw and Rutledge⁴ Erganian and Wade^{6c} Ferris⁷ Villaret and Martiny¹⁴ⁱ Ferris and Wilkins^{14l} Burwell^{14m} Hussey¹⁴ⁿ Rutledge and Gray^{14o} Veal and Hussey^{14p} Gray and Skinner^{14q} Eyster and Middleton^{14r}

16 Ehrlich, Ballon, and Graham² Rutledge and Gray^{14o} Gray and Skinner^{14q}

cava is not supported by the findings of the aforementioned authors or by those of the present study. The additional studies made here of arm to lung, femoral vein to lung and lung to brain times show that the slowing is on the venous side of the circulation in the upper part of the body, Hitzig^{14h} also found some slowing on the venous side in his patients.

The significance of the slowed venous circulation time may be different under various circumstances. Since the arm to tongue and arm to lung time represent time elapsed during the passage of blood from a vein to the end organ, it cannot be determined from this measurement whether the blood is flowing slowly or is taking a long and circuitous path through the inferior cava or both. In this connection it is of interest that patient 3 of the present study showed a slight fall in venous pressure and a return of the arteriovenous oxygen difference to normal, with no change in circulation time. It is considered, therefore, that the first measurements made on this patient are a reflection of stasis, while the results of the later studies suggest that enough collateral circulation developed to overcome the stasis, the prolonged circulation time on this occasion being an indication of the length of the pathway back to the heart. It should be borne in mind also that elevation of the venous pressure consequent to obstruction does not necessarily indicate slowing of flow in the obstructed vein or in the capillaries draining into it. Stewart¹⁷ has shown that such obstruction may cause the flow of blood to decrease initially, with a return to normal when enough pressure has been built up in the veins.

In all 3 of the patients described by Arrillaga and Taquini,^{6a} in 1 (no 1) of the 5 described by Ferris⁷ and in all 3 studied here while manifesting respiratory symptoms, studies of the arteriovenous oxygen difference indicate stasis in the tissues drained by the superior cava. On the other hand, in 4 (nos 2, 3, 4 and 5) of Ferris' patients⁷ with no respiratory symptoms and in 1 (patient 3) studied here after spontaneous improvement of symptoms, the observations show that no stasis in the tissues existed, apparently because an adequate venous collateral circulation had developed. The development of this collateral circulation, with a resultant late fall in venous pressure toward normal some time after ligation of the superior vena cava, has been studied in the dog by Carlson¹⁸.

17 Stewart, G. N. Studies on the Circulation in Man. I. Measurement of the Bloodflow in the Hands, *Heart* **3** 33, 1911, The Effect of Bandaging of the Legs on the Rate of Blood Flow in the Feet, *Arch Int Med* **19** 335 (March) 1917.

18 Carlson, H. A. Obstruction of the Superior Vena Cava, *Arch Surg* **29** 669 (Oct) 1934.

The data of the present study and of the earlier work reviewed provide the basis for an understanding of the mechanism of the signs and symptoms occurring in patients with obstruction of the superior vena cava. The cyanosis in all patients with the syndrome is consequent to increased prominence of the cutaneous veins¹⁹ and in many is accentuated by abnormally great deoxygenation of capillary blood due to stasis, arterial unsaturation caused by obstruction to breathing is not a factor in the uncomplicated case, as was pointed out by Arrillaga and Taquini.^{6a} The edema of the upper part of the body is at least in part the result of high venous pressures. The role of high filtration pressures in the genesis of edema has been studied by Landis²⁰ and others.²¹ Nevertheless the fact that in spite of high venous pressures the edema may be intermittent^{14g} or completely absent^{21a} suggests that anoxia due to stasis may also be a factor.

The respiratory manifestations of obstruction of the superior cava seen in the patients studied here consisted of periodic breathing, constant hyperventilation, dyspnea at rest and on exertion and orthopnea. The observation of periodic breathing is not surprising. Its occurrence in patients with increased spinal fluid pressure is well known, and it has been produced in animals by raising the intracranial pressure.²² Increases in the latter always result when the venous pressure in the head is high. Burger^{14g} and Porot^{14g} found the spinal fluid pressure increased in a patient with obstruction of the superior vena cava, and Ferris⁷ later made the same observation in his 5 patients, these earlier findings are corroborated in the present study (table 2). However, only 1 of Ferris' 7 patients had "periods of

19 Goldschmidt, S., and Light, A. B. Cyanosis, Unrelated to Oxygen Unsaturation, Produced by Increased Peripheral Venous Pressure, *Am J Physiol* **73** 173, 1925.

20 Krogh, A., Landis, E. M., and Turner, A. H. The Movement of Fluid Through the Human Capillary Wall in Relation to Venous Pressure and to the Colloid Osmotic Pressure of the Blood, *J Clin Investigation* **11** 63, 1932. Landis, E. M., Jonas, L., Angevine, M., and Erb, W. The Passage of Fluid and Protein Through the Human Capillary Wall During Venous Congestion, *ibid* **11** 717, 1932. Landis, E. M., and Gibbon, J. H. The Effects of Temperature and of Tissue Pressure on the Movement of Fluid Through the Human Capillary Wall, *ibid* **12** 105, 1933.

21 Mende. Ueber Hyperämie und Oedem bei der Hemmung des Rückflusses des venösen Blutes durch die Staubinde, *Deutsche Ztschr f Chir* **150** 379, 1919. Drury, A. N., and Jones, N. W. Observations upon the Rate at Which Oedema Forms When the Veins of the Human Limb Are Congested, *Heart* **14** 55, 1927.

21a Hinshaw and Rutledge.⁴ Smirk^{14t}

22 Greeley, C. E., and Greeley, P. O. Circulatory Changes During Periodic Ventilation with Apnea Produced by Marked Curtailment of Blood Flow to the Brain, *Am J Physiol* **95** 263, 1930.

hyperpnea." As was pointed out by Arrillaga and Taquini,^{6a} patients with obstruction of the superior vena cava show lowering of the level of carbon dioxide in the arterial blood, the observations made here on the amount of carbon dioxide in the alveolar air are in accord with their findings. The importance of lowered levels of carbon dioxide in the arterial blood in the genesis of periodic breathing is generally accepted.²¹ Anoxia of the respiratory center must exist in many patients with obstruction of the superior vena cava, but the role of such anoxia in the causation of periodic breathing is not established.^{23c} No attempt will be made to explain the occurrence of paroxysmal dyspnea in this syndrome, since it is not clear from the published reports²⁴ whether the phenomena observed were true paroxysmal dyspnea or merely a manifestation of periodic breathing.

The possible relation of impaired flow through the respiratory center to hyperventilation, dyspnea and orthopnea in cardiac decompensation has been the subject of much controversy, in spite of the demonstration that in animals slow flow through the brain causes hyperventilation^{25a}, in addition Calhoun and others^{25b} observed increased respiratory activity after jugular obstruction in human beings. Accordingly, the occurrence of these symptoms in persons in whom there is stasis in the brain and not in the lungs is of great importance. In the work of Arrillaga and Taquini,^{6a} as well as in the present study, there is a striking correlation between the occurrence of hyperventilation, dyspnea and orthopnea and changes in the gases of the blood which are indicative of stasis in the upper part of the body. This finding is in harmony with the data of Ferris,⁷ who noted no

such respiratory abnormalities and no evidence of cerebral stasis in most of his patients with obstruction of the superior vena cava. The relationship between stasis in the tissues and hyperventilation is especially well illustrated by patient 3 of the present study. The disappearance of symptoms in this patient was paralleled by the disappearance of evidences of tissue stasis apparently as a consequence of the development of collateral circulation, while the venous pressure and the circulation time showed no striking change. It might be objected that in the patients of the present series respiratory symptoms may have developed because of the presence of masses of appreciable size within the thorax, as evidenced by roentgenographic findings and by low vital capacities. However, the latter showed little or no change when hyperventilation disappeared. Moreover, in many of the reported cases with respiratory manifestations²⁶ the cause of the obstruction of the superior vena cava was either thrombosis or pressure by a mass far too small to interfere with pulmonary function.

Another possible objection to the acceptance of slow flow through the brain as a cause for the dyspnea and hyperventilation studied here may be found in the reports that distention of the great veins may cause reflex hyperventilation.²⁷ However, the work on which the latter conclusion is based is not entirely acceptable in that conclusive proof is lacking that slowing of flow through the brain did not occur in those experiments. Moreover, in some of the reported cases in which dyspnea and orthopnea occurred, for instance, case 1 of Ochsner and Dixon,³ distention of the superior cava could not have occurred because the vein was thrombosed in its entire length. It is therefore concluded that the weight of evidence favors the opinion expressed by Arrillaga and Taquini^{6a} that a cause of hyperventilation and dyspnea in the syndrome of obstruction of the superior vena cava is slowed flow leading to tissue stasis in the respiratory center. Since the stasis is aggravated by recumbency, orthopnea is readily understandable. In the case of those patients in whom dyspnea is present only on exertion, it is likely that the general rise in venous pressure accompanying exercise de-

23 (a) Pembrey, M. S., and Allen, R. W. Observations upon Cheyne-Stokes Respiration. *J. Physiol.* **32** xviii, 1905. (b) Douglas, C. G., and Haldane, J. S. The Causes of Periodic or Cheyne-Stokes Breathing, *ibid.* **38** 401, 1909. (c) Anthony, A. J., Cohn, A. E., and Steele, J. M. Studies on Cheyne-Stokes Respiration, *J. Clin. Investigation* **11** 1321, 1932. (d) Harrison, T. R., King, C. E., Calhoun, J. A., and Harrison, W. G., Jr. Congestive Heart Failure. XX Cheyne-Stokes Respiration as the Cause of Paroxysmal Dyspnea at the Onset of Sleep, *Arch. Int. Med.* **53** 891 (June) 1934.

24 Arrillaga and Taquini^{6a} Lian and Abaza^{6b} Erganian and Wade^{6c} Ferris⁷

25 (a) Greeley and Greeley²² Gesell, R. The Chemical Regulation of Respiration, *Physiol. Rev.* **5** 551, 1925. Schmidt, C. F. The Influence of Cerebral Blood-Flow on Respiration. I. The Respiratory Responses to Changes in Cerebral Blood-Flow, *Am. J. Physiol.* **84** 202, 1928. (b) Calhoun, J. A., Cullen, G. E., Harrison, T. R., Wilkins, W. L., and Tims, M. M. Studies in Congestive Heart Failure. XIV Orthopnea. Its Relation to Ventilation, Vital Capacity, Oxygen Saturation and Acid-Base Condition of Arterial and Jugular Blood, *J. Clin. Investigation* **10** 833, 1931.

26 Ehrlich, Ballou, and Graham² Ochsner and Dixon³ Hinshaw and Rutledge⁴ Erganian and Wade^{6c} Rutledge and Gray^{14b} Gray and Skinner^{14a}

27 Harrison, T. R., Harrison W. G., Jr., Calhoun, J. A., and Marsh, J. P. Congestive Heart Failure. XVII The Mechanism of Dyspnea on Exertion, *Arch. Int. Med.* **50** 690 (Nov.) 1932. Harrison, T. R., Harrison W. G. Jr. and Marsh J. P. Reflex Stimulation of Respiration from Increase in Venous Pressure, *Am. J. Physiol.* **100** 417, 1932. Megibow, R. S., Katz, L. N., and Feinstein, M. Kinetics of Respiration in Experimental Pulmonary Embolism, *Arch. Int. Med.* **71** 536 (April) 1943.

creases the differential between the high pressure above the obstruction and the lower pressure below it necessary for the maintenance of flow through the collateral vessels, thereby aggravating the stasis in the brain. A corollary to the foregoing conclusion is that cerebral stasis is a cause of hyperventilation and dyspnea in cardiac decompensation, it is considered that the concept that increased venous pressure favors orthopnea²⁸ is supported by the results of the present study. It is not to be concluded, however, that congestion of the lungs may be minimized as a factor in the symptoms of cardiac decompensation, the role of the pulmonary changes in congestive failure in the causation of hyperventilation and dyspnea²⁹ and of orthopnea³⁰ has been discussed at length elsewhere.

It has been shown³¹ that orthopnea in patients with cardiac disease is aggravated by a high

28 Ernstene, A. C., and Blumgart, H. L. Orthopnea: Its Relation to Increased Venous Pressure of Myocardial Failure, *Arch Int Med* **45** 593 (April) 1930.

29 Altschule, M. D. The Pathological Physiology of Chronic Cardiac Decompensation, *Medicine* **17** 75, 1938.

30 Altschule, M. D., Zamcheck, N., and Iglauer, A. The Lung Volume and Its Subdivisions in the Upright and Recumbent Positions in Patients with Congestive Failure. Pulmonary Factors in the Genesis of Orthopnea, *J Clin Investigation* **22** 805, 1943.

31 Harrison, W. G., Jr. The Cisternal Pressure in Congestive Heart Failure and Its Bearing on Orthopnea, *J Clin Investigation* **12** 1075, 1933; Cerebrospinal Fluid Pressure and Venous Pressure in Cardiac Failure and the Effect of Spinal Drainage in the Treatment of Cardiac Decompensation, *Arch Int Med* **53** 782 (May) 1934; Robertson, H. F., and Fetter, F. The Effects of Venesection on Arterial, Spinal Fluid and Venous Pressures with Especial Reference to Failure of the Right and Left Heart, *J Clin Investigation* **14** 305, 1935.

spinal fluid pressure, and accordingly the question arises as to whether high intracranial pressure might not be the cause of the orthopnea occurring with obstruction of the superior vena cava. However, the aforementioned parallelism between the presence of orthopnea and the evidences of stasis and the lack of close correlation between the occurrence of that symptom and high spinal fluid pressures suggest that at most intracranial pressure exerts only a contributory influence. In addition, it has been shown³² that elevation of the intracranial pressure may by itself slow the flow of blood through the brain.

SUMMARY AND CONCLUSIONS

A study of the respiratory and cardiovascular dynamics in 5 patients with obstruction of the superior vena cava revealed that hyperventilation, with a consequent fall in alveolar carbon dioxide, often occurs in this syndrome. Stasis may be present in the brain of a patient with obstruction of the superior vena cava. High venous pressure and slowed circulation time do not necessarily indicate the presence of stasis. Studies of the blood gases are more helpful in this regard.

It is concluded that the occurrence of hyperventilation, dyspnea, orthopnea or periodic breathing in a patient with obstruction of the superior vena cava is associated with tissue stasis in the brain.

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32 Wolff, H. G., and Blumgart, H. L. The Cerebral Circulation. VI. The Effect of Normal and of Increased Intracranial Cerebrospinal Fluid Pressure on the Velocity of Intracranial Blood Flow, *Arch Neurol & Psychiat* **21** 795 (April) 1929.

PRIMARY ATYPICAL PNEUMONIA OF UNKNOWN CAUSE, WITH UNUSUAL MANIFESTATIONS AND COMPLICATIONS

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The growing volume of reports¹ concerning primary atypical pneumonia attests to the interest in this condition. It is not a contagious disease, but it does occur in epidemic form, which may account for the actual increase in the number of cases. Furthermore, the attention which has been focused on the disease has revealed cases that otherwise might have been overlooked. It is noteworthy that the 150 cases of pneumonia² which form the basis of this report were derived from a total of 180 cases of pneumonia of all types encountered at an army station hospital from Sept 1, 1942 to June 1, 1943. In view of our clinical experience, five sixths seems to be a high proportion of unclassifiable pneumonia, which may in part be due to the younger age group of the patients.

Among these 150 cases certain unusual manifestations appeared, as follows: meningismus in 3 cases, pleural effusion in 4, marked leukopenia in 1, spontaneous pneumothorax and simulating tuberculosis in 1, pulmonary abscess in 4 and late secondary infection in 2.

CASES WITH MENINGITIS

CASE 1—History—A white man aged 24 was admitted to the hospital on Nov 29, 1942 and discharged on Dec 19. His past history was irrelevant. The present illness began three days before he entered the hospital, with abrupt onset of shaking chills, weakness, pains in the muscles of the legs, back and ankles and

1 Reimann, H A, Havens, W P, and Price, A H. Etiology of Atypical ("Virus") Pneumonia with a Brief Resume of Recent Discoveries, *Arch Int Med* 70 513 (Oct) 1942. Dingle, J H, Abernethy, T J, Badger, G F, Buddingh, G J, Feller, A E, Langmuir, A D, Rueggsegger, J M, and Wood, W B, Jr. Primary Atypical Pneumonia, Etiology Unknown, *War Med* 3 223 (March) 1943. Campbell, T A, Strong, P S, Grier, G S, III, and Lutz, R J. Primary Atypical Pneumonia. A Report of Two Hundred Cases at Fort Eustis, Virginia, *J A M A* 122 723 (July 10) 1943.

2 The diagnosis of primary atypical pneumonia was applied in cases in which there was definite pulmonary involvement on roentgenography, frequently with severe headache and leukocytosis with a white cell count not exceeding 15,000, and in which pneumococcic and other types of pneumonia were excluded by laboratory data or the clinical course.

cough productive of green sputum. Severe pounding frontal headache began four hours before his admission and nausea the night before.

Physical Examination—The patient was acutely ill, with his skin flushed and his lips cyanotic. He had no cutaneous lesions. There was moderate stiffness of the neck. He kept his eyes partly closed, although he said he did not suffer from photophobia. A slight nasal discharge and conjunctival injection were noted. The chest was clear. There was no cardiovascular disease. The Kernig sign was slightly positive.

Laboratory Examinations—At a lumbar puncture made on November 29, the fluid flowed more freely than normally. It contained 1 lymphocyte per high power field, the globulin was not increased, the total protein content was 25.6 mg per hundred cubic centimeters and the sugar content 80 mg, the Wassermann reaction was negative and the colloidal gold curve 0000000000, culture gave negative results. On December 2 there were 6 lymphocytes per high power field, the globulin was not increased, the sugar content was 74 mg per hundred cubic centimeters, and there was no growth on culture. On December 6 the fluid contained 3 lymphocytes per high power field, the sugar content was 70 mg per hundred cubic centimeters, the globulin was not increased, and culture gave negative results. Blood counts were as follows: November 30, 85 per cent hemoglobin, 4,400,000 erythrocytes and 13,750 leukocytes, with 65 per cent polymorphonuclear cells, 30 per cent lymphocytes and 5 per cent eosinophils; December 2, 9,000 leukocytes, with 73 per cent polymorphonuclear cells, 26 per cent lymphocytes and 1 per cent eosinophils. On December 3 the sputum showed occasional pneumococci. Culture and the Kahn test of the blood gave negative results. Culture of material from the throat showed no meningococci.

Roentgenograms of Chest—On November 29, a triangular area of infiltration was seen in the upper lobe of the left lung. Five days later this area was still present and in addition a small area was present in the upper lobe of the right lung. Twelve days after the second examination the chest was almost entirely clear.

Course—The temperature on the patient's admission was 104 F, it rose to 105 F the same day and then came down, by lysis, to normal by the sixth day. There was a slight rise to 99.6 F on the thirteenth, fourteenth and fifteenth days of the illness, coinciding with sore throat. Culture of material from the throat at that time showed hemolytic streptococci, and the white blood cell count was 12,000. The pulse rate was 100 to 110 and then dropped to normal with the temperature. The respiratory rate was 25 to 30 for three days and then became normal. The patient was lethargic on admission and hazy mentally. This condition, together with the headache, completely disappeared in about a week. His cough became much more productive, and rales devel-

oped at the bases of both lungs and over the left upper quadrant of the chest. On the fourth day the chest was clear on physical examination. The stiffness of the neck was gone in a week. The patient's feeling of well-being returned, together with his appetite, on about the sixth day in the hospital, this improvement coinciding with a drop of temperature to normal. He received sulfadiazine, 7 Gm the first day, 6 Gm a day on the second, third, fourth, fifth and sixth days and 4 Gm on the seventh, eighth and ninth days.

This case illustrates, additionally, the complete ineffectiveness of sulfadiazine therapy in primary atypical pneumonia and infection of the throat by secondary invaders late in the disease.

CASE 2—A white man aged 26 was admitted to the hospital on Nov 15, 1942 and discharged December 11.

History—The past history was irrelevant. His present illness began two days before his admission, with sudden onset of severe postorbital pounding headache, cough, shaking chills and perspiration. His throat was slightly sore. He had anorexia, and his "stomach felt weak." There were cramps in the calves of the legs and once, on the day of the patient's admission, in the right thigh.

General Examination—The patient was mentally confused, repeating words and phrases both of the questions and of his answers. He was slightly disoriented and complained of vertigo. There was no stiffness of the neck. Definite photophobia was noted, and the conjunctivas and scleras were injected. The blood pressure was 115 systolic and 80 diastolic. Both calves were tender, and the feet were held in the extended position and resisted flexion, which, however, could be accomplished with effort. The reflexes were hyperactive. The right knee jerk was greater than the left, the Oppenheim sign was present on the left side, and the Kernig sign was also elicited.

Laboratory Examination—Lumbar puncture was done on November 16. The spinal fluid obtained contained 6 lymphocytes per high power field, the globulin was not increased, the total protein content was 42 mg per hundred cubic centimeters, the colloidal gold curve was 1111100000, the Wassermann reaction was negative. On November 23 a second lumbar puncture was done. The fluid then contained 33 lymphocytes per high power field, the sugar content was 63 mg per hundred cubic centimeters, the globulin was increased, and culture gave negative results. On November 16 the sputum was found to contain a few pneumococci, not typable. Blood counts were as follows: November 16, 12,000 leukocytes, with 72 per cent polymorphonuclear cells, 26 per cent lymphocytes and 2 per cent monocytes; November 23, 9,650 leukocytes, with 69 per cent polymorphonuclear cells, 23 per cent lymphocytes, 2 per cent monocytes and 6 per cent eosinophils; November 25, 85 per cent hemoglobin, 4,800,000 erythrocytes and 14,400 leukocytes, with 75 per cent polymorphonuclear cells, 24 per cent lymphocytes and 1 per cent eosinophils; November 30, 14,000 leukocytes; December 2, 8,800 leukocytes, with 72 per cent polymorphonuclear cells, 23 per cent lymphocytes, 1 per cent monocytes and 4 per cent eosinophils. The Kahn reaction of the blood was negative.

Roentgenograms of Chest—On November 16 there was a triangular area of infiltration in the mesial portion of the base of the right lung. Eleven days later the infiltration was more extensive. It cleared in about ten more days.

Course—The temperature on the patient's admission was 105 F, it came down to normal in three days, then rose to 104 F on the fifth day and followed a

remittent course from normal up to 101 or 102 F through the eleventh day. It became normal on the twelfth day. The pulse rate was 120 the first day and came down to normal along with the temperature. The respiratory rate was normal throughout.

On the third day, the patient had diminished breath sounds at the base of the right lung and was still confused mentally. During the night he had restless sleep with a short period of hallucinations. On the fifth day, with rise of temperature, mental confusion increased and there was slight stiffness of the neck, with headache, vertigo and photophobia persistent. On the eighth day, the neck was still slightly stiff, there were slight headache and a little drowsiness but no photophobia. On the ninth day, after a lumbar puncture the previous day, all symptoms improved. On the tenth day, the patient suffered from slight headache and vertigo only when sitting up, there was no photophobia. On the twelfth day—the cough had been increasing all week—vesicular breath sounds and rales were present at the base of the right lung. Since the ear drums were red, administration of sulfadiazine was started. On the seventeenth day, the patient's mental condition was rapidly improving, and his family said that he seemed completely normal mentally again.

This case is of particular interest because of the presence of leukocytes in the spinal fluid. Additionally, it illustrates secondary infection of the middle ear late in the disease.

THREE CASES WITH PLEURAL EFFUSION

These cases are of interest mainly from the roentgenologic point of view, but clinically it was noted that they were usually the cases of severe symptoms with a good deal of prostration, a high, remittent type of fever and a strong tendency to relapse, especially if the patient was allowed to get out of bed before the fluid had been completely resorbed.

CASE 3—A white man aged 27 was admitted to the hospital on Dec 4, 1942 and discharged on Feb 9, 1943.

History—The patient had had pneumonia four years previously, in the right lung. For one week the patient had had a "head cold," and for twenty-four hours before admission he had suffered from cough, severe headache and generalized malaise. Just prior to admission he had a shaking chill and sharp pain in the lower part of the chest on the right side.

Physical Examination—The patient was prostrated. He had a nasal discharge and suppression of breath sounds at the base of the right lung.

Laboratory Examinations—Culture of the sputum on December 5 revealed no pneumococci. On January 3 there was an abundant growth of hemolytic staphylococci, on January 18, of *Staphylococcus aureus*. Leukocyte counts were as follows: December 5, 8,500; December 12, 9,300; December 19, 15,500; December 26, 13,400, with 72 per cent polymorphonuclear cells; January 14, 16,050, with 81 per cent polymorphonuclear cells; January 22, 11,000; January 27, 8,550. The urine and the Kahn reaction of the blood were normal. An electrocardiogram made on December 29 showed sinus tachycardia.

Roentgenograms of the Chest—On December 5 a hazy area at the base of the right lung was seen, which was consistent with atypical pneumonia, six days later the

infiltration was denser and more extensive, one month later (fig 1) the infiltration was still present and there was a small amount of fluid. The chest finally became normal nine weeks from the onset.

Course—The patient's temperature on admission was 100 F. It fluctuated between normal and 103 F for the first fifteen days, stayed around 99 F until the twenty-second day, again fluctuated up to 103 F until the thirty-third day and then dropped to normal and remained so.

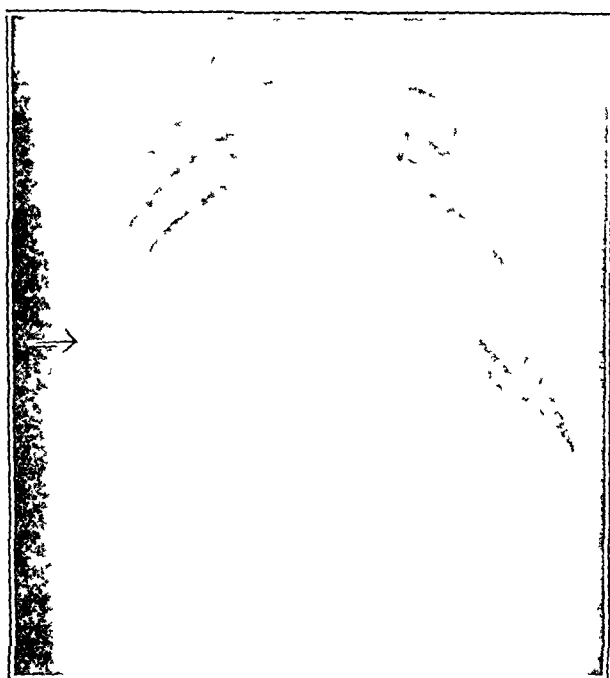


Fig 1 (case 3)—Fluid at the base of the right lung still present one month after the onset of pneumonia.

CASE 4—A white man aged 30 was admitted to the hospital on March 14, 1943 and discharged on April 3.

History—The past history was irrelevant. He had had a dry cough for four days and for one day had suffered from acute malaise, a temperature of 104 F and increased cough. He was given 5 Gm of sulfathiazole the day before admission.

Physical Examination—The right sclera was injected. The pharynx was red, and there was a slight nasal exudate. The lungs showed dulness, bronchial breath sounds and rare post-tussive rales at the base of the left lung.

Laboratory Examinations—The sputum showed untypable pneumococci. Blood counts were as follows: March 15, white blood cells 15,000 and polymorphonuclear cells 73 per cent; March 22, white blood cells 15,850 and polymorphonuclear cells 88 per cent; March 26, white blood cells 8,700. The urine was normal, and the Kahn reaction of the blood was negative. Roentgenograms of the chest on March 15 showed infiltration at the base of the left lung consistent with atypical pneumonia. Five days later there was infiltration on both sides with a small amount of fluid at the base of the left lung. In eleven more days the chest was normal.

Course—The patient's temperature on admission was 102 F, and it dropped to normal the next day. It then rose daily from normal to 101 F for seven days until March 20, when it rose to 103 to 105 F for forty-eight hours. This last rise in temperature coincided with the appearance of pains in the joints and a generalized morbilliform eruption consistent with a drug eruption. Administration of sulfathiazole, which had been given

in a dose of 6 Gm daily since the patient's admission, was discontinued, and the fever, rash and arthralgia disappeared in two days. The physical signs became more pronounced during the first seven days, but by the eleventh day there remained only dulness and diminished bronchovesicular breath sounds at the base of the left lung. At that time the cough was minimal, and it disappeared shortly thereafter.

CASE 5—A white man aged 22 was admitted to the hospital Nov 12, 1942 and discharged Jan 27, 1943.

History—His past history was irrelevant. About two days before admission he noted chilliness, slight sore throat, frontal headache and a mild, nonproductive cough. The dizziness diminished, but the other symptoms progressed.

Physical Examination—The patient was acutely ill. He was chilly and felt dizzy when upright. His lips were dry, his tongue was coated, and crusting was present around the nares. Left external strabismus was present. There was no nystagmus or stiffness of the neck. The blood pressure was 95 systolic and 65 diastolic.

Laboratory Examinations—Lumbar puncture was done on November 14. The globulin was not increased, the fluid contained 5 lymphocytes per cubic millimeter, the colloidal gold curve was 1111000000, the Wassermann reaction was negative, and the protein content was 34 mg per hundred cubic centimeters. Culture of material from the left ear on Jan 18, 1943 yielded *Staph albus*. Blood counts are shown in the table.

Roentgenograms of the Chest—On November 13 a hazy infiltration consistent with atypical pneumonia and accumulation of the fluid was seen at the base of the



Fig 2 (case 5)—Fluid at the base of the right lung nine days after the onset of the illness.

White Blood Cell Counts in Case 5

Date	White Cells	Mature Granulo cytes, %	Stab Cells, %	Immature Granulo cytes, %	Lym pho cytes, %	Large Lym pho cytes, %	Imma ture Lym pho cytes, %
11/14	2,200	0	16	43	16	19	5
11/16	3,600	0	15	38	19	8	19
11/17	2,300	0	31	27	14	8	14
11/20	3,800	6	48	19	15	0	2
11/21	6,500	6	40	6	17	5	24
11/24	10,950	11	38	11	32	2	3
12/29	7,400	40	25	3	26	0	0
1/25	5,800	10	49	0	33	0	0

right lung This increased in extent for one week (fig 2) but began to clear two weeks after the onset At the end of three weeks a small amount of fluid was present at the base of the right lung, but this was gone one week later The entire chest was not clear until nine weeks after the onset

Course—The patient's temperature was normal on his admission but rose to 105 F the next day Thereafter there was a remittent fever with temperature from 100 to 105 F until November 21, when the temperature dropped to normal It stayed normal until December 10 During that period the following events occurred On November 14 the vertigo had disappeared, the cough had increased and rales appeared at the base of the right lung On that day the patient had a short period of stiffness of the neck with questionably positive Kernig and Brudzinski signs A lumbar puncture was done, the pressure was 160 mm and the fluid was clear He complained of pleuritic pain in the right side of the chest and had diminished bronchovesicular breathing sounds at the base of the right lung and in the right anterior portion of the chest with rales in the latter area On November 18, he had rales to the level of the sixth thoracic vertebra posteriorly on both sides, with bronchovesicular sounds over the same areas The toxicity decreased, and he was mentally clearer On November 24, the cough continued, and pleuritic pain returned, with a definite leathery rub in the lower part of the right axilla On November 29, the rub was gone but pleuritic pain was still present On December 10, the temperature rose to 101 F It then had a remittent course from 99 to 104 F through December 16, when it dropped by lysis, reaching a normal level by December 18 On December 10 the patient complained of pain in the right shoulder During the next five days rales appeared in the right infraclavicular region, with bronchovesicular breath sounds and sibil, but these signs subsequently disappeared On Jan 9, 1943, his temperature suddenly rose to 103 F for one day On January 10, he complained of nasal discharge and sore throat Physical examination showed follicular patches in the throat During the next three days he complained of pain in both ears, and the left showed bullous inflammation of the tympanic membrane, which was incised with drainage of pus Sulfathiazole was given from January 13 through January 22, during which time the discharge from the ear subsided

This case illustrates an unusual complication of the hemopoietic system as well as pleural effusion The white blood cell count rose on the day of defervescence, but the abnormal cells persisted longer The patient was allowed to be up before the fluid was completely absorbed, and he promptly had a relapse, which was accompanied by spread to the upper lobe of the right lung without further hemopoietic complications

CASE OF PNEUMONIA SIMULATING TUBERCULOSIS WITH DEVELOPMENT OF SPONTANEOUS PNEU- MOTHORAX WHILE PATIENT WAS ASYMPTOMATIC

CASE 6—A white man was admitted to the hospital July 9, 1943 and discharged July 29

History—The past history was irrelevant The patient was admitted because of mental depression and suicidal ideas, present for two or three weeks

Physical Examination—The patient seemed essentially normal

Laboratory Findings—The white blood cells numbered 8,900 per cubic millimeter, with polymorphonuclear leukocytes 72 per cent and lymphocytes 28 per cent The hemoglobin content was 89 per cent The urine was normal The sedimentation rate (determined by the Wintrobe method) was normal The sputum repeatedly failed to yield tubercle bacilli

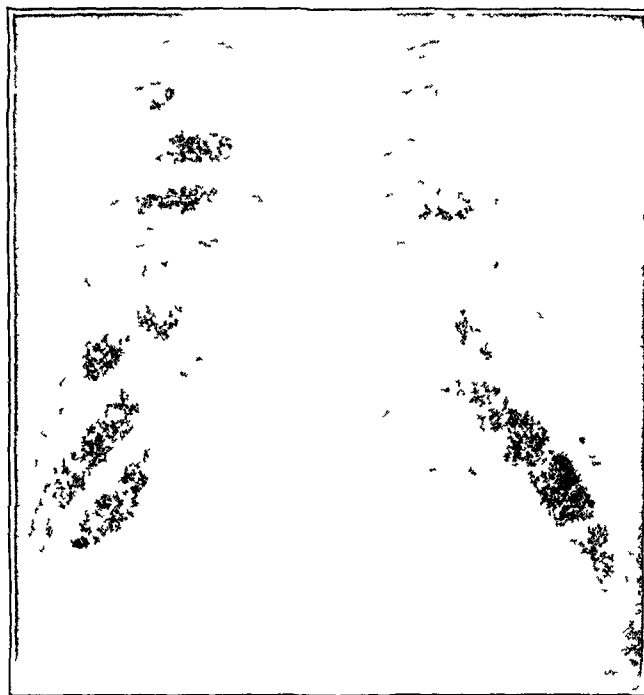


Fig 3 (case 6)—Mottled infiltration in the right upper pulmonary field simulating tuberculosis

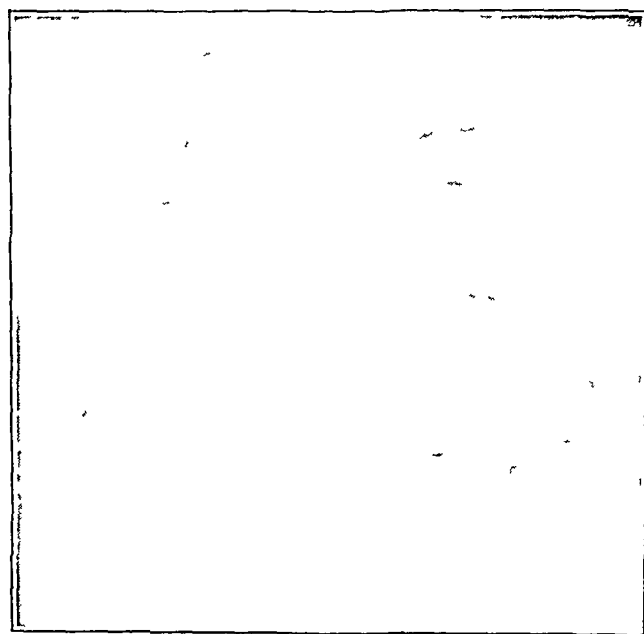


Fig 4 (case 6)—Later film than that of figure 3, showing a small spontaneous pneumothorax at the apex of the right lung

Progress—The temperature was normal on the patient's admission but peaked to 99 F on the first two afternoons It was subsequently normal when the patient was kept at rest in bed No cough was observed during his hospitalization A diagnosis of manic-depressive psychosis was made, and he was transferred to another institution

Roentgenograms of Chest—Of greatest interest were the roentgenograms of the chest The one on July 23 (fig 3) showed a soft cottony infiltration in the right in-

fraclavicular region extending out into the first interspace from the hilus. Subsequent roentgenograms, made after the patient's discharge to another hospital, showed (fig 4) complete clearing of the infiltration, but a small apical pneumothorax had appeared, extending down as far as the first and second interspaces.

THREE CASES OF APUTRID PULMONARY ABSCESS WHICH RESOLVED PROMPTLY AND ONE CASE OF SECONDARY INFECTION WITH PULMONARY ABSCESS, EMPYEMA AND DEATH WITH AUTOPSY

CASE 7—A white man aged 29 was admitted to the hospital on Jan 11, 1943 and discharged March 10.

History—The patient had been a stone cutter. For two weeks before admission he suffered from cough associated with pain in the right side of the chest at the region of the right nipple. Five days before admission he was confined to quarters with a temperature of 100.2 F, mostly in the afternoon. He had been raising a couple of spoons of sputum daily,



Fig 5 (case 7)—Aputrid abscess cavity in the right upper pulmonary field nineteen days after the onset of cough.

and four days before his admission the sputum had been blood streaked. He had not had chills or sweats.

Physical Examination—The chest was clear. There was a varicocele on the left side. The patient was not acutely ill.

Laboratory Examinations—The sedimentation rate on February 19 was 0.3 mm. On January 12 there were 9,250 white cells. On February 23 the red cells numbered 5,000,000. There was no subsequent leukocytosis. Five three-day concentrates of the sputum for tubercle bacilli failed to reveal any. On February 2 a heavy growth of viridans streptococci was obtained, on February 9, hemolytic staphylococci, gram-negative diplococci and nonhemolytic streptococci. On January 9 the gastric washings failed to reveal tubercle bacilli on smear. A culture of material from the throat taken January 30 yielded nonhemolytic streptococci and gram-negative diplococci. The urine and the Kahn reaction of the blood were negative.

Roentgenograms of the Chest—On January 9 there was a hazy infiltration in the upper lobe of the right lung which was consistent with atypical pneumonia. One week later an area of rarefaction was present in the center of that area, and this was thought to represent an abscess (fig 5). The area of infiltration and the abscess rapidly resolved, and in about one month the chest was clear.

Course—From January 11 through January 14, the temperature varied from normal to 99.6 F. On January 15 it suddenly rose to 102.6 F, but it came down to 99 F by January 19. Then it fluctuated from normal to 100 F through February 3, when it returned to normal. It stayed normal until February 11, and then fluctuated between 97 and 99 F daily throughout the remainder of the course. No abnormal physical signs were found at any time. A tuberculin test done on February 13 with 0.01 mg of old tuberculin elicited a negative reaction, a test on February 15, with 0.1 mg gave a positive reaction. The patient brought up only a small amount of sputum, never especially purulent or foul.

CASE 8—A white man aged 25 was admitted to the hospital April 9, 1943 and discharged May 4.

History—He had had pneumonia when he was 19. One week before admission he had noted onset of headache, malaise and chill. This was followed by a running nose, slight sore throat and a dry cough, which soon became productive of white phlegm. For three days before admission he had had hoarseness. The headache persisted up to his admission, although the nasal discharge had disappeared.

Physical Examination—The patient had a slight nasal discharge. There was no dulness or altered breath sounds, but there were sibilant and moist rales anteriorly from the right clavicle down to the fifth rib and laterally to the anterior axillary line. The blood pressure was 105 systolic and 65 diastolic.

Laboratory Examinations—The sputum on April 20 failed to show tubercle bacilli by smear or on inoculation of a guinea pig. The sedimentation rate of the blood on April 30 was 0.4 per minute. Blood counts were as follows: April 9, white cells 24,500, with polymorphonuclear cells 79 per cent; April 13, white blood cells 13,150; April 28, white blood cells 7,700, with polymorphonuclear cells 68. The urine was normal. The Kahn reaction of the blood was negative.

Roentgenograms of the Chest—On April 10, roentgen examination showed a large area of infiltration involving the hilar zone and the lower portion of the upper lobe of the right lung, which was thought to be pneumonia. Five days later an area of rarefaction consistent with abscess appeared in the same lobe. Twelve days later, or seventeen days after the first film was made, the lung showed almost complete clearing.

Course—The temperature, which was 100.2 F on the patient's admission, rose to 104.8 F the same day and then gradually came down to normal in eight days. On the eighth day, administration of sulfadiazine was started because of roentgen findings of pulmonary abscess, 6 Gm daily was given through the tenth day, and 4 Gm a day from the eleventh through the twentieth day, a total of 58 Gm. On April 11, there were medium moist rales over the entire upper lobe of the right lung. On April 16, only a few post-tussive rales were heard just lateral to the right third and fourth costochondral junctures. On April 18, the cough had diminished, although the patient was bring-

ing up small amounts of nonfoul green sputum. Throughout his stay he had a complaint of a constant aching pain in the right upper quadrant of the chest, which disappeared, along with the cough, by April 19.

CASE 9—A white man aged 38 was admitted to the hospital Dec 15, 1942 and discharged Jan 19, 1943.

History—His past history was irrelevant. For two days he had suffered from chilly feelings, running nose, cough, occipital headache and a few mild aches in the legs. Sore throat had been present for twelve hours.



Fig 6 (case 9)—A putrid abscess at the base of the left lung sixteen days after the onset of cough. Note the fluid level.

Physical Examination—The pharynx was diffusely red, the tonsillar lymph nodes were enlarged. There were a few coarse rales at the base of the left lung.

Laboratory Examinations—Blood counts were as follows: December 15, white cells 7,000, with 74 per cent polymorphonuclear cells; December 21, white blood cells 15,000; January 12, white blood cells 9,000; January 22, white blood cells 8,000. The urine was normal.

Roentgenograms of the Chest—On December 16 the roentgenogram was normal. Seven days later there was a dense infiltration at the base of the left lung. Six days after this an area of rarefaction appeared in the same location, which was thought to represent an abscess (fig 6). The base of the lung gradually cleared, but the abscess remained for two weeks. At the end of another month, the chest had cleared entirely.

Course—The temperature on the patient's admission was 101.6 F. It came down to normal by lysis by December 19. It rose abruptly to 104 F on December 20 and came down remittently by lysis to normal on January 1. The respiratory rate was never above 24. Administration of sulfadiazine was started on December 31 and continued through January 12. The rales heard on admission disappeared, but on January 2 reappeared at the base of the right lung. On January 15, in spite of positive roentgen findings, physical examination revealed nothing significant. The patient generally had a mild cough, and he felt poorly only from December 21 through January 2. On the latter date he felt much better and there was very little cough remaining. Sputum was minimal and mucoid.

CASE 10—A white man aged 30 was admitted to the hospital Dec 4, 1942 and died Jan 16, 1943.

History—The family and the past history were irrelevant. For three days the patient had had fever, with temperature up to 103 F, malaise, backache, chilly sensations and mild, nonproductive cough.

Physical Examination—The patient was uncomfortable but not acutely ill. He had an occasional dry cough, and his skin was flushed. The conjunctivas were injected. The throat was slightly inflamed. The lungs were normal. The pressure was 106 systolic and 70 diastolic.

Laboratory Examinations—An electrocardiogram taken on January 11 showed a rate of 111, a PR interval of 0.14 second, slight deviation of the axis to the right, and a diphasic T wave in lead III. The interpretation was beginning deviation of the axis to the right, probably associated with subacute pulmonary disease. Cultures of material from the throat revealed the following organisms: December 5, staphylococci and gram-negative diplococci; December 7, untyped pneumococci; December 10, hemolytic and nonhemolytic streptococci; January 15 and 19, hemolytic streptococci and *Staphylococcus albus*. Cultures of blood revealed: January 19, gram-negative diplococci and streptococci; post mortem, January 30, pure growth of hemolytic streptococci. Culture of material from the lungs showed: January 30, left lung, pure growth of hemolytic streptococci, and right lung streptococci and *Staph aureus haemolyticus*. Blood counts were as follows: December 4, white cells 8,900, with 74 per cent polymorphonuclear cells; December 14, white cells 11,000, with polymorphonuclears 78 per cent; December 22, white cells 13,000, with polymorphonuclears 91 per cent; December 26, white cells 14,500, with polymorphonuclears 89 per cent; January 1, white cells



Fig 7 (case 10)—Infiltration of the right pulmonary field five days after the onset of severe primary atypical pneumonia.

20,000, with polymorphonuclears 82 per cent; January 5, white cells 25,000; January 12, white cells 27,000, with polymorphonuclears 92 per cent; January 14, white cells 30,000, with polymorphonuclears 93 per cent. The urine was normal, and the Kahn reaction of the blood was negative.

Roentgenograms of the Chest—On December 6, a light hazy area was seen in the right hilar zone (fig 7).

This increased rapidly in size, and in about a week the entire right lung was involved, together with the upper lobe and the base of the left lung. The fine splotchy infiltration involving both lungs cleared somewhat at times, but about 60 per cent of both lungs remained involved for about a month. At this time, which was six weeks from the onset, an abscess developed at the apex of the right lung (fig 8). The major portion of both lungs still showed a dense stringy infiltration throughout.

Course—The temperature on the patient's admission was 103 F. It fluctuated remittently from 99 to 105 F through December 11 and then gradually dropped by lysis to 99 F on January 12, when it rose to 102 F abruptly. Thereafter it ran from 99 to 104 F until the patient's death, January 16. On December 6, the patient complained of headache and dulness and rales were noted at the base of the right lung. On December 10, the respiratory rate, which had been 20 to 25, rose suddenly to 32. On December 11, the cough was more productive, the sputum was mucopurulent, there was only slight cyanosis, and the spleen was palpable 2 fingerbreadths below the costal margin. On December 15, the cyanosis was worse, and breathing was labored. On December 25, the patient was placed in an oxygen

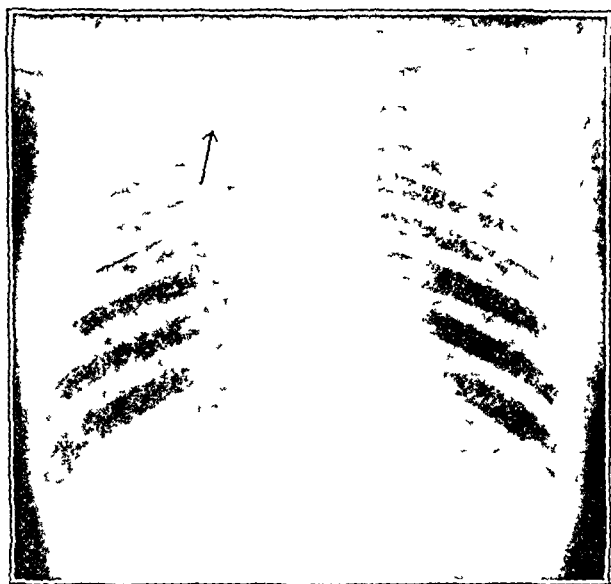


Fig 8 (case 10)—Pulmonary abscess six weeks from the onset of the illness. Note the fluid level.

tent, coarse moist rales were noted over his chest. On December 28, he felt better, and an oxygen mask was substituted for the tent, although the respiratory rate was still 25 to 30. From January 6 on, the oxygen was gradually withdrawn. The only complaint was occasional pleuritic pain. On January 11, the patient had an attack of syncope, associated with pain in the right side of the chest. Examination of the chest revealed nothing abnormal. An electrocardiogram was taken January 14 (see report of laboratory examinations). On January 15, the patient appeared worse, his appetite was poor, he felt pain in the left side of the chest, and there were rales at the bases of both lungs and in the right axilla. On January 16, the patient declined rapidly, became pulseless, brought up much frothy sputum and died. Sulfadiazine was administered from December 5 through December 12, but this treatment was stopped because of red blood cells and casts in the urine. After clearing of urine the drug was readministered from December 17 through December 22.

Gross Observations at Autopsy—Thoracic Cavity. There were numerous fine adhesions all over the right lung and at the base of the left lung. The right lung weighed 1,025 Gm, on section, the upper lobe was firm and yellowish to pink gray and the lower lobe was nodular with yellow purulent exudate in the larger bronchi and the dilated bronchioles. In the upper lobe near the apex an abscess cavity 4 by 3 by 2 cm was found, it contained thick yellow purulent exudate and its walls were covered with a shaggy yellow-gray layer of fibrin and necrotic tissue. No direct connection between this cavity and the smaller bronchi could be demonstrated. The left lung weighed 755 Gm. The upper lobe was normal, and the lower lobe was dark reddish gray with yellow-gray exudate in the bronchi and bronchioles. The hilar nodes bilaterally revealed a bulging, succulent, pinkish gray surface.

Microscopic Observations at Autopsy—Bronchus and Peribronchial Lymph Node. Section revealed moderate edema of the lymph node with increased proliferation of mononuclear and reticular cells in the sinusoids. There were also rare accumulations of neutrophils in the sinusoids.

Right Lung. Several sections of the right lung revealed the pleura to be covered with a thick layer of fibrin containing many neutrophils and a few macrophages. The pleura was edematous, with the capillaries engorged, and was infiltrated with many neutrophils and macrophages. Some sections of the slide showed the alveoli to be filled with variable numbers of red cells, neutrophils, mononuclears and macrophages in a fibrin meshwork. In some regions the cellular exudate consisted almost entirely of red cells and neutrophils, while in others mononuclears and lipid-laden macrophages predominated. The alveolar walls were swollen and infiltrated with mononuclears. In other areas the cellular exudate showed beginning organization with ingrowth of capillaries and fibroblasts. The wall of the abscess cavity, noted on gross examination, consisted of a layer of fibrin and degenerating exudate overlying a wall of juvenile connective tissue and budding capillaries which in turn was heavily infiltrated with mononuclears, lipid-laden macrophages, plasma cells and occasional neutrophils and foreign body type giant cells. Besides this large abscess cavity there were many small abscesses consisting of large focal accumulations of neutrophils with destruction of all intervening alveolar walls. *Left lung*. The pleura was essentially normal. The bronchioles contained a fibrinous exudate in which were desquamated epithelium and many neutrophils and mononuclears. Their walls were edematous and infiltrated with many mononuclears and neutrophils and occasional foreign body type giant cell. One bronchiole showed beginning organization of its fibrinous exudate by ingrowth of capillaries and juvenile connective tissue. Many of the peribronchial alveoli showed a hemorrhagic infiltration. Other alveoli contained edema fluid, and variable numbers of red cells, neutrophils and macrophages in a fibrin meshwork. In other regions lipid-laden macrophages replaced the red cells and neutrophils. Occasional small areas were found in which the exudate showed signs of organization.

In analyzing the course of these patients with pulmonary abscess, it was seen that this complication occurred on the nineteenth, the thirteenth, the sixteenth and the forty-second day of their respective illnesses. In additional cases of atypical pneumonia without abscess formation it

was noted that the leukopenia present on the patients' admission was succeeded by a moderate leukocytosis (15,000 to 18,000 white cells) during the afebrile period of the convalescence, about the eighteenth day. Sometimes this was associated with an increased amount of sputum.

TWO CASES ILLUSTRATING OCCURRENCE OF FEVER, LEUKOCYTOSIS, SPREAD OF THE PNEUMONIA AND PROMPT RESPONSE TO TREATMENT WITH SULFONAMIDE COMPOUNDS DURING CONVALESCENT STAGE OF THE DISEASE

CASE 11—A white man aged 21 was admitted to the hospital on June 30, 1943 and discharged July 26.

History—His family and his past history were irrelevant. For four days he had had nonproductive cough, feverishness, severe postorbital headache and temperature as high as 101 F.

Examination—Physical examination revealed a dry, coated tongue and dulness, bronchial breath sounds and bronchophony at the base of the right lung.

Examination of the sputum on June 30 and July 14 failed to reveal pneumococci. Leukocyte counts were as follows: June 30, 14,300 with 80 per cent polymorphonuclear cells, July 1, 8,900, with 73 per cent polymorphonuclear cells, July 10, 21,550, July 12, 18,500 with 85 per cent polymorphonuclear cells, July 14, 13,800, July 17, 7,400.

Roentgenograms of the chest revealed the following significant features: June 30, a dense hazy area at the base of the right lung, July 5, the area of haziness more extensive, with a small amount of fluid present, July 12, 50 per cent clearing of the base of the right lung and a small area of infiltration at the base of the left lung, July 17, all abnormalities diminishing, July 23, complete clearing.

Course—The cough, distressing at the onset, gradually subsided. The initial temperature of 101 F dropped to normal on the fifth day of the patient's hospitalization (eighth day of the illness), but there was another rise to 99 to 101 F during the tenth to fifteenth day of the hospitalization (fourteenth to nineteenth day of the illness), coincidental with the rise of the white blood cell count to 21,550 on July 10. These changes were unaccompanied by increase in the cough.

This case illustrated a spread of the infection on the tenth day of the patient's hospitalization (fourteenth day of the illness), accompanied by definite leukocytosis, probably indicative of invasion by secondary organisms, in contrast to the lack of leukocytosis at the onset.

CASE 12—A white man aged 24 was admitted to the hospital on Nov 24, 1942 and discharged on December 27.

History—The family and past history were irrelevant. For two days the patient had had cough, productive of yellow sputum, pain in the right shoulder and fever.

Examination—Physical examination revealed a slightly inflamed pharynx and bronchovesicular breath sounds posteriorly over the left side of the chest at the level of the fifth to eighth thoracic vertebrae.

Blood culture on December 13 gave negative results. Leukocyte counts were as follows: November 25, 7,900, December 13, 21,600, with 91 per cent polymorphonuclears, December 19, 8,100. Culture of the

sputum on November 26 revealed gram-negative diplococci, smear failed to reveal pneumococci, on December 8, a smear did not show any tubercle bacilli. Roentgenograms of the chest on November 25 showed a dense infiltration in the medial third of the left lung extending out from the hilus, on December 12, slight residual infiltration was still present.

Course—The cough and sputum increased for several days after the patient's admission to the hospital, and rales spread all over the lower half of the left side of the chest posteriorly. Simultaneously with the drop in temperature during the first eleven days of the hospitalization (thirteen days of the illness), the cough and physical signs began to clear. On December 13, (eighteenth day of hospitalization or twentieth of illness), he had a chill and a rise of temperature, together with return of cough and purulent sputum and signs of consolidation at the base of the right lung. All the signs and symptoms cleared rapidly in three days under sulfadiazine therapy.

This case illustrated again a spread of pulmonary infection late in the convalescence, accompanied by leukocytosis.

COMMENT

In many respects the complaints referable to the central nervous system that have been noted, e.g. stiffness of the neck, headache, disorientation, vertigo and strabismus, make one think of pneumonia in children, since these symptoms rarely usher in an attack in adults. Cunningham³ reported such symptoms in 8 per cent of 1,500 children with pneumonia. Adams and Berger⁴ stated that 48 per cent of 145 children with pneumonia were admitted to the hospital with a diagnosis of meningitis. However, involvement of the central nervous system such as was evident in cases 1, 2 and 5 has been previously noted by others⁵ in atypical pneumonia, though details were not always given. Reimann^{5a} mentioned 5 such cases, in 1 of which (case X) there was a spinal fluid cell count of 350, of which 75 per cent were polymorphonuclears, and the total protein measured 74 mg per hundred centimeters. Kneeland^{5c} reported 1 patient (out of 52 with atypical pneumonia) with stiff neck and stupor.

3 Cunningham, A. R. Results of Open Air Treatment of Pneumonia in Children. An Analysis of 1,500 Cases of Lobar Pneumonia from the Records of the Children's Hospital, Boston, Boston M & S J **174**: 753 (May 25) 1916.

4 Adams, F. D., and Berger, B. J. Differential Diagnosis of Lobar Pneumonia and Appendicitis in Children, J A M A **79** 1809 (Nov 25) 1922.

5 (a) Reimann, H. A. An Acute Infection of the Respiratory Tract with Atypical Pneumonia, J A M A **111** 2377 (Dec 24) 1938. (b) Gallagher, J. R. Acute Pneumonitis. A Report of Eighty-Seven Cases Among Adolescents, Yale J Biol & Med **13** 663 (May) 1941. (c) Kneeland, Y., Jr., and Smetena, H. F. Current Bronchopneumonia of Unusual Character and Undetermined Etiology, Bull Johns Hopkins Hosp. **67** 229 (Oct) 1940. (d) Allen, W. H. Acute Pneumonitis, Ann Int Med **10** 441 (Oct) 1936.

whose spinal fluid contained only 4 cells. It is important to bear in mind that stupor, stiff neck and disorientation may occasionally dominate the clinical picture of this disease at the onset, especially in view of the paucity of physical signs of the pulmonary involvement that so often exists during the first week.

Small amounts of pleural fluid have been mentioned in other reports. For example, Smiley and associates,⁶ in a report of 86 cases, said that "in about 5 per cent of the cases the involvement was severe. In this group there was a decided tendency to some involvement of the interlobar pleura and, in one case, of the parietal pleura." In a report of 132 cases of pneumonia in college students Murray⁷ found 1 case with "x-ray evidence of questionable fluid." Our patients with fluid (cases 3, 4, 5 and 10) were all moderately or severely ill. In all of them the fluid absorbed slowly without tapping the chest. We did notice a tendency to relapse or spread of the parenchymal infection in the patients with pleural involvement, especially when they were allowed to become ambulatory too soon. Case 5, with the leukopenia and marked outpouring of immature cells, seems to be unique, for no such complication has been previously reported. Prompt return of the blood picture to normal coincided with defervescence. It is interesting that the patient did have a mild leukocytosis with the late secondary infection of his throat and ear and that sulfathiazole was used at that time without adverse effect on his blood.

The 3 cases with apurid pulmonary abscess (cases 7, 8 and 9) are similarly unlike those reported elsewhere. The resemblance of the condition to tuberculous cavitation, especially when located in the upper pulmonary fields, is noteworthy, but such a cause was ruled out in our cases by the clinical course and laboratory studies. The pathogenesis seems to be that of infection by secondary invaders during the convalescent period of the disease. Examples of such invasion of the throat (case 1) and the middle ear (case 2) as well as the lungs without abscess formation (cases 11 and 12) are given. Such superinfections are accompanied by leukocytosis, in contradistinction to the primary disease. Moreover, the use of sulfonamide compounds at such times has the same therapeutic effectiveness as with primary bacterial infections, whereas their ineffec-

tiveness in primary atypical pneumonia is now well recognized. Finally, it cannot be overemphasized that if such apurid abscesses are encountered in the future, the benign course in our cases should be borne in mind and surgical intervention should certainly be withheld in favor of conservative therapy.

Our 1 fatality was in a case (case 10) of primary atypical pneumonia of great severity and superimposed secondary infection at a time when the patient was debilitated though recovering from the primary disease. This is the type of situation that occurs frequently in debilitating chronic disease of all kinds, however, it has been noted in primary atypical pneumonia previously,⁸ with empyema, pulmonary abscess and extension of the pneumonia after invasion by streptococci or staphylococci. The incidence of such a severe complication is extremely low in this disease. In fact, Kneeland and Smetana^{5c} said of secondary bacterial infection: "Our clinical impression was that secondary bacterial infection of the lungs occurred so rarely as to make it seem that the disease might actually predispose against it." It does not seem justified to advocate the routine use of full doses of sulfonamide compounds from the onset of treatment of atypical pneumonia in order to prevent the aforementioned late complications, since complications due to these drugs are more frequent and more dangerous than secondary bacterial complications.

If it is considered worth while to attempt to prevent late secondary bacterial complications, it is suggested that the drug should be given after the first week and in relatively small, nontoxic doses, such as 3 Gm per day for adults.

SUMMARY

Of 180 cases of all varieties of pneumonia reported in a nine month period among soldiers, 150 were classified as instances of primary atypical pneumonia.

Complications noted were 3 instances of meningismus, 3 of pleural effusion, 1 of extreme leukopenia, 1 of spontaneous pneumothorax, 3 of benign pulmonary lung abscess and 1 of fatal pulmonary abscess and empyema among 10 patients.

An attempt was made to elucidate the pathogenesis and treatment of the pulmonary abscesses occurring during the course of primary atypical pneumonia.

6 Smiley, D. F., Showacre, E. C., Lee, W. F., and Ferris, H. W. Acute Interstitial Pneumonitis: A New Disease Entity, *J. A. M. A.* **112** 1901 (May 13) 1939.

7 Murray, M. E., Jr. Atypical Bronchopneumonia of Unknown Etiology, Possibly Due to a Filterable Virus. *New England J. Med.* **222** 565 (April 4) 1940.

8 Adams, J. M., Green, R. G., Evans, C. A., and Beach, N. Primary Virus Pneumonitis: A Comparative Study of Two Epidemics, *J. Pediat.* **20** 405 (April) 1942. McKinlay, C. A., and Cowan, D. W. Acute Respiratory Infections, Including Lobar Pneumonia and Atypical Pneumonia in a Young Adult Group, *Journal-Lancet* **61** 125 (April) 1941.

EFFECT OF PROLONGED PHYSICAL INACTIVITY ON TOLERANCE OF SUGAR

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It is recognized that exercise increases the utilization of dextrose. This fact was first demonstrated by Rakestraw¹ and by Levine² and their associates, who observed in normal people that a long period of exercise is usually accompanied by a drop in the level of sugar in the blood, although short, strenuous exercise increases the concentration of sugar in the blood. Exercise also lowers the level of blood sugar of persons with diabetes who have an adequate supply of insulin. This effect is so striking that exercise³ is now accorded a prominent place in the treatment of diabetes along with diet and insulin. In contrast, there has been no work to show the effect of physical inactivity or prolonged rest in bed on the carbohydrate metabolism in nondiabetic persons. The fact that exercise increases the carbohydrate metabolism does not necessarily mean that inactivity will do the opposite. If such reasoning were followed one would expect to find an improved carbohydrate tolerance in normal thin persons taking insulin to gain weight. However, this is not the case, since in a large number of these persons a diminished sugar tolerance has been found⁴ during the period of treatment with insulin.

Nearly all of the adults were studied at the Jewish Memorial Hospital, where Dr Rudolph Haas and Dr Israel R. Duke assisted. The children were studied at the New England Peabody Home for Crippled Children through the courtesy of Dr Frank R. Ober and Dr Gerald N. Hoeffel, Boston.

1 Rakestraw, N. W. The Effect of Muscular Exercise upon Certain Common Blood Constituents, *J. Biol. Chem.* **47** 565, 1921. Rakestraw, N. W., Barley, C. V., and Hahn, Y. D. Further Changes in Some of the Blood Constituents Following Strenuous Muscular Exercise, *ibid.* **56** 121, 1923.

2 Levine, S. A., Gordon, B., and Derick, C. L. Some Changes in the Chemical Constituents of the Blood Following a Marathon Race with Special Reference to the Development of Hypoglycemia, *J. A. M. A.* **82** 1778 (May 31) 1924. Gordon, B., Kohn, L. A., Levine, S. A., Matton, M., Scriver, W. M., and Whiting, W. B. Sugar Content of the Blood in Runners Following a Marathon Race, *ibid.* **85** 508 (Aug. 15) 1925.

3 Joslin, E. P., Root, H. F., White, P., and Marble, A. The Treatment of Diabetes Mellitus, ed. 7, Philadelphia, Lea & Febiger, 1940, p. 333.

4 Blotner, H. Insulin and Sugar Tolerance in Thin People, *Arch. Int. Med.* **53** 153 (Jan) 1934.

It seemed of practical interest to study this problem by observing whether the carbohydrate metabolism was disturbed in a group of non-diabetic patients who had been confined to bed for relatively long periods of time. This would appear to be of particular importance now, since many persons injured in the war will be confined to bed for considerable periods and the problem of interpreting values for sugar tolerance for some of them will undoubtedly arise.

This paper reports the results of dextrose tolerance tests obtained in 86 nondiabetic persons—70 adults and 16 children—who had been long in bed because of certain diseases.

PLAN OF INVESTIGATION

Since the simplest test available at present to determine the integrity of the mechanism of carbohydrate metabolism is that for dextrose tolerance, this test was used. The values for dextrose tolerance of patients who had been in bed in the hospital from four weeks to eight years were compared with observations made on 10 normally active adults and on 11 active children. A standard dose of 100 Gm of dextrose was used for the adults. The dose was 50 Gm for a child who weighed less than 75 pounds (34 Kg) and 75 Gm for one who weighed more than 75 pounds. The dextrose was mixed with 250 cc of water, flavored with 50 cc of lemon juice, chilled and ingested after the patient had fasted overnight. The concentration of sugar in the blood and in the urine was determined in specimens taken during fasting and at intervals of one-half hour and one, two and three hours after the ingestion of the dextrose mixture. The determinations⁵ of the blood sugar were made in all cases on 0.1 cc samples of capillary blood according to the micro-method of Folin and Malmros⁶. Simultaneous determinations of capillary and of venous blood sugar were made for all of the children and for 18 inactive and 10 active adults in order to study the arteriovenous differences in the blood sugar. The capillary and venous bloods were obtained by two operators simultaneously from the antecubital veins and from the finger tips. The venous blood was mixed with powdered sodium oxalate, and then immediately 0.1 cc of this blood was treated like capillary blood.

The test for sugar in the urine was made with Benedict's solution. In 24 cases the sugar tolerance tests were repeated under the same conditions, on one

5 Miss Muriel Reiner gave technical assistance.

6 Folin, O., and Malmros, H. An Improved Form of Folin's Micro Method for Blood Sugar Determinations, *J. Biol. Chem.* **83** 115, 1929.

to three occasions after varying intervals to see whether there would be any changes in the results. In 10 cases the sugar tolerance tests were made after the formerly bedridden patients had been ambulatory for two to six months.

When it was found that so many of the adult inactive patients had a diminished sugar tolerance and that age may have been a factor in these results, the sugar tolerance of a group of 16 inactive children was studied.

CLINICAL MATERIAL

There were studied first 70 consecutive nondiabetic patients, 36 men and 34 women. Most of the patients were of normal or slightly below normal weight for their height, age and sex. The weight of a few patients was above or below normal. The 4 heaviest patients weighed 175 pounds (79 Kg) each. Nearly all of these patients and those of the control group were Jewish. Their ages varied from 18 to 92 years, as follows: Seven patients were from 18 to 41 years old, 12, from 41 to 51 years, 16 from 51 to 61 years, 21, from 61 to 71 years, and 12, from 71 to 78 years, 2 were 80 and 92 years old respectively.

The patients received the routine house diet, which consisted of approximately 250 Gm of carbohydrate, 70 Gm of protein and 75 Gm of fat. The daily intake was approximately 2,000 calories, with an adequate amount of protective foods. The adults had various pathologic conditions, such as hereditary ataxia, polycythemia, tuberculous spondylitis, amyotonia atrophica, progressive muscular dystrophy, syringomyelia, the tabetic form of dementia paralytica, progressive muscular atrophy, multiple sclerosis, old cerebral hemorrhage, hemiplegia, atrophic arthritis, chronic myocarditis, coronary occlusion, hypertension, carcinoma of the bowel, bronchiectasis, fractured leg or hip, peptic ulcer, periarteritis nodosa, gout, lymphoblastoma, Parkinson's disease, amputation of both legs or of one leg, chronic colitis, and cancer of the lung or prostate. A moderate hypertension, with the blood pressure about 185 systolic and 95 diastolic, was present in 12 cases.

Practically all of these patients had been in bed for a considerable time before admission to the hospital. Before the sugar tolerance tests were made the patients had been confined to bed in the hospital as follows: 22 patients from one to four months, 20 from five to ten months, 21 from one to four years, 5 from five to seven years and 2 for eight years.

The children, all gentiles, had been confined to bed from seven months to thirteen years. There were 10 boys and 6 girls, their ages ranging from 4 to 13 years. Most of them were in casts or on traction. They had such conditions as tuberculosis of the spine and knee, Legg's disease, scoliosis, coxa vara, clubbed foot, inflammation of the hip, necrosis of the femur, old poliomyelitis, arthritis and progressive muscular dystrophy. They ate well and took a good general diet. Only 2 of the children appeared considerably overweight for their height.

In view of the results of the sugar tolerance tests, careful family histories with regard to diabetes were taken in all of the cases. It is interesting to note that a family history of diabetes was obtained for only 2 adult patients (3 per cent of the total number), each of these patients had 2 brothers with diabetes. None of the children had a history of diabetes in the

family. This familial incidence of diabetes of 3 per cent is less than that found by Blotner and Hyde⁷ for consecutive volunteers and selectees, 5.2 per cent of whom had a family history of diabetes.

RESULTS IN ADULTS

The results obtained in the adults and in the children are shown in the accompanying charts.

The criteria for interpreting the normal sugar tolerance are rather difficult to fix, because of the variable blood sugar curves which have been reported for so-called nondiabetic persons and consequently labeled normoglycemic curves. One of the best papers on the criteria for determining the normal sugar tolerance was written by Gray,⁸ who studied 300 apparently healthy persons. His data showed the average normal fasting blood sugar to be 0.09 per cent and the average postprandial values to be 0.14 per cent in one-half hour, 0.12 per cent in one hour, 0.11 per cent in two hours and 0.09 per cent in three hours. These values remained the same after the ingestion of 50 to 100 Gm of dextrose. Others have reported higher values for normal sugar tolerance curves, which may have been obtained from patients with chronic diseases.

In general, there was a diminished sugar tolerance in the patients who had been confined to bed for considerable periods. Of the 70 adults, 63 had definitely diminished sugar tolerance curves. Typical examples of the results of these curves tests are shown in chart 1. The fasting blood sugar ranged from 70 to 130 mg per hundred cubic centimeters in 37 cases it was from 70 to 105 mg, in 20 from 106 to 124 mg and in 6 approximately 130 mg.

One hour after the ingestion of dextrose the blood sugar rose to abnormal levels, the maximum being 364 mg per hundred cubic centimeters. At this time 34 patients had concentrations of blood sugar ranging from 180 to 225 mg, 22 had approximately 250 mg and 7 had 290 to 364 mg. In two hours the levels of blood sugar decreased appreciably in some cases, and in a few they increased. In three hours 16 patients had levels of blood sugar of 120 mg or less, and 47 had levels ranging from 140 to 278 mg. In all of these cases the specimens of fasting urine contained no sugar. After the ingestion of dextrose considerable amounts of

7 Blotner, H, and Hyde, R W. Renal Glycosuria in Selectees and Volunteers, *J A M A* 122 432 (June 12) 1943, Studies in Diabetes Mellitus and Transient Glycosuria in Selectees and Volunteers, *New England J Med* 229 885 (Dec 9) 1943.

8 Gray, H. Blood Sugar Standards. I. Normal and Diabetic Persons, *Arch Int Med* 31 241 (Feb) 1923.

sugar, varying from 1+ to 4+, were found often in the urine. However, it was quite striking to find that frequently the urine was free from sugar when simultaneous levels of blood sugar were 200 or 250 mg. This condition was found on repeated occasions even for the same persons. Apparently there was a high renal threshold for sugar in these cases. Often the patients who were in bed for the longest periods had the highest blood sugar curves. Some of the patients who were more active in their life

RESULTS IN CHILDREN

The results of sugar tolerance tests of 16 inactive children were of unusual interest because here too the tolerance was diminished, particularly as compared with the results obtained for the 11 normally active gentle children. However, the children's sugar tolerance curves did not rise as high as those of the adults. Typical examples of the sugar tolerance curves obtained for children are shown in chart 3. The fasting levels of blood sugar of the children

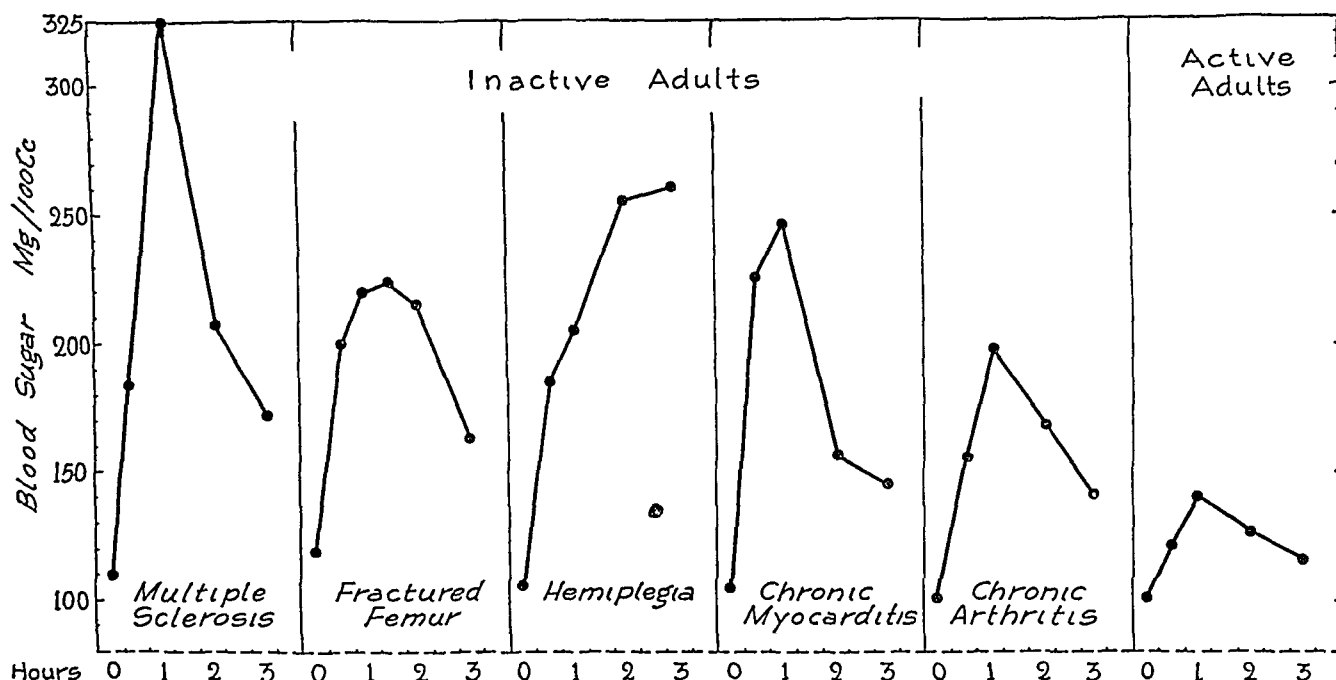


Chart 1—Illustrations of blood sugar curves following the ingestion of 100 Gm of dextrose for 63 nondiabetic adults with various diseases who had been confined to bed from one month to eight years

in bed or in chairs did not have as greatly elevated blood sugar curves as those who were more restricted in activity. These rules, however, were not invariable. Hypertension, infection, arteriosclerosis and obesity in themselves did not appear to be significant in bringing about these results.

The age and sex did not appear to have any definite bearing on the dextrose tolerance in these cases, because a number of the patients between 18 and 50 years of age had abnormal results of the tests, whereas 10 active persons aged 53 to 73 had normal results. One arthritic patient aged 67 years who had been in bed for seven years had a normal sugar tolerance. In most cases in which sugar tolerance tests were repeated on several occasions under similar conditions there was almost no variation in the results.

For 10 patients who had been confined to bed for long periods sugar tolerance tests were repeated after they had been ambulatory from two to six months. The blood sugar was found to be normal in 6 cases, somewhat improved, although still abnormal, in 2 cases, and unchanged in 2 cases (chart 2).

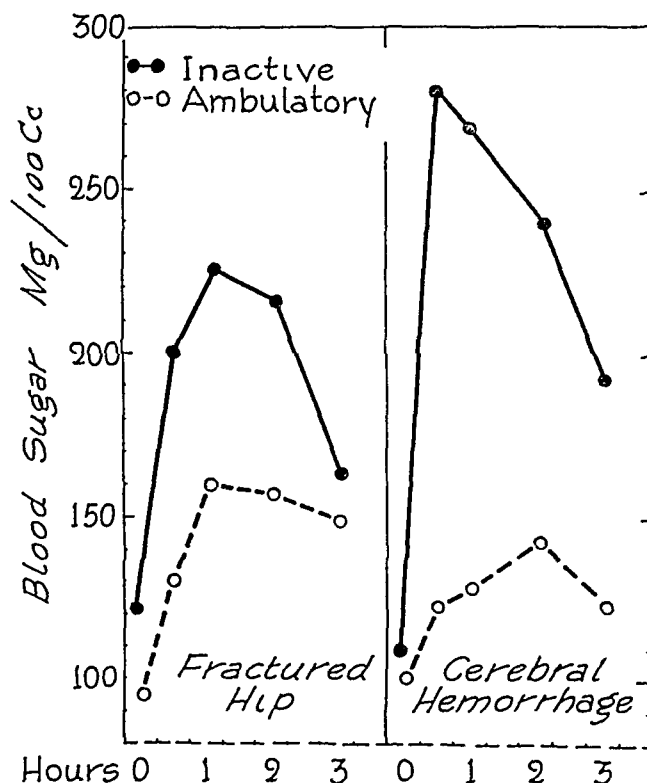


Chart 2—Comparison of results of sugar tolerance tests of some patients when they were confined to bed and after they had been ambulatory for several months

ranged from 90 to 107 mg per hundred cubic centimeters. The greatest rise in the blood sugar one hour after the ingestion of dextrose was to 238 mg, which decreased to approximately 140 to 172 mg in two hours and to 90 to 145 mg in three hours. The specimens of fasting urine of the children showed no sugar. After the ingestion of dextrose some of the subjects had varying amounts of sugar in the urine. Some of the children seemed to have a diminished renal threshold for sugar, since sugar (1 plus and 2 plus) was found in the urine when the blood sugar was at a level of from 115 to 167 mg

ARTERIOVENOUS DIFFERENCE IN BLOOD SUGAR

It had been suggested that the lack of muscular activity or lack of muscular utilization of sugar was the cause for the abnormal results obtained in the sugar tolerance tests. If this were the case

Blistein,¹³ even in the presence of considerable arteriovenous differences. In addition, Langner and Fies⁹ found this to be true whether there is a free flow of blood from the finger or whether the finger is squeezed. Consequently, in this paper I refer to the sugar in the capillary blood as arterial blood sugar.

The results of the tests for arteriovenous differences appeared quite significant after the ingestion of dextrose. These results are illustrated in chart 4.

In the inactive adults the usual arteriovenous difference in the fasting blood sugar was approximately 8 or 10 mg per hundred cubic centimeters. A few had equal values for arterial and the venous fasting blood sugar, and in others the venous content was 3 or 4 mg higher than the arterial. At the peak of the blood sugar curves after the ingestion of dextrose the arteriovenous differences of the blood sugar generally ranged

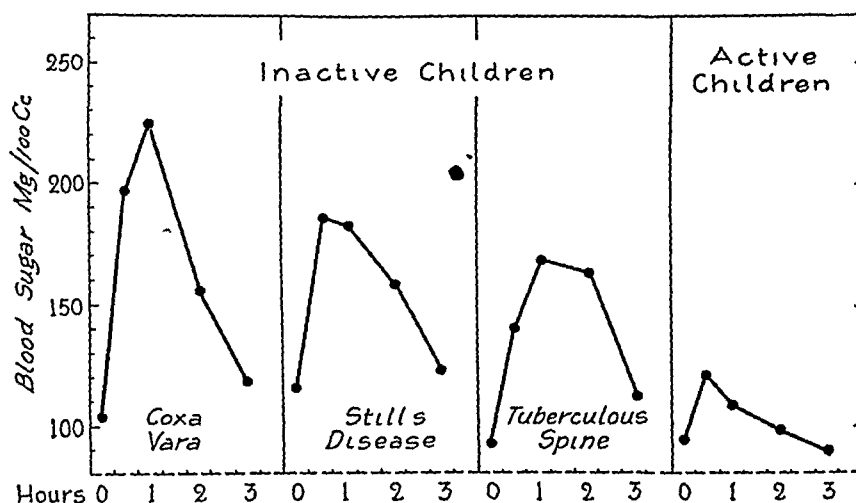


Chart 3—Characteristic blood sugar curves following the ingestion of dextrose for 16 nondiabetic children with certain diseases who had been confined to bed from six months to thirteen years, compared with typical sugar tolerance in active children.

one would expect the physically inactive patients to have diminished differences in the simultaneous values for arterial and for venous blood sugar.

To study this aspect of the problem further the arteriovenous difference in the blood sugar was studied in 18 inactive adults and 16 inactive children and compared with the normal difference. For practical purposes the concentration of sugar in the blood obtained from the capillaries of the finger by puncture is practically identical with the concentration of sugar in the blood simultaneously obtained from the radial artery. This has been well demonstrated by Langner and Fies,⁹ Hagedorn,¹⁰ Foster,¹¹ Jonas¹² and

from 15 to 30 mg per hundred cubic centimeters, and on rare occasions the difference was as much as 40 to 50 mg. In three hours the arteriovenous difference in the blood sugar was approximately 15 or 20 mg. In comparison, the active adults after the ingestion of dextrose had arteriovenous differences of the blood sugar of 10 to 20 mg at the peak of the blood sugar curves and of approximately 10 mg in three hours.

10 Hagedorn, H. C. Om sukkerprocenten i vena mediana cubiti, *Ugeskr. f. Læger* **82** 796, 1920.

11 Foster, G. L. Studies on Carbohydrate Metabolism. I. Some Comparisons of Blood Sugar Concentrations in Venous Blood and in Finger Blood, *J. Biol. Chem.* **55** 291, 1923.

12 Jonas, L. A Note on Cutaneous Venous Blood Sugar Difference in Normal Males and Females and in Thyroid Disease, *J. Clin. Investigation* **12** 139, 1933.

13 Blistein, I. La glycémie artérielle et veineuse, *Arch. internat. de med. exper.* **8** 25, 1933.

9 Langner, P. H., and Fies, H. L. Blood Sugar Values of Blood Obtained Simultaneously from the Radial Artery, Antecubital Vein, and the Finger, *Am. J. Clin. Path.* **12** 559, 1942.

In the children the arteriovenous differences in blood sugar were similar to those found in the adults, as illustrated also in chart 4

In many of the patients with diminished sugar tolerance the arteriovenous differences were even greater than those ordinarily found in normal persons. This strongly suggests that even though patients are physically inactive their muscles utilize sugar normally. Consequently, the result obtained in the inactive patients requires another explanation

COMMENT

The results of this investigation show that persons with certain pathologic conditions who are confined to bed for considerable periods have diminished dextrose tolerance. The blood sugar curves are of the diabetic type. It might be assumed that because of the physical inactivity the muscles do not use up as much dextrose as

necessity for secreting insulin, and the insulin content of the pancreas is reduced. Consequently, the reaction of the islets of the pancreas to stimulation by dextrose becomes less than normal. Furthermore, with physical inactivity there is not the demand for rapid storage and utilization of sugar that is present in active persons, and this results in less demand on the pancreas and ultimately in diminished function of the pancreas.

There have been reports of tests showing diminished sugar tolerance in patients with certain diseases who have been ill for some time. Although the cause for this is unknown, attempts were made to correlate the disease with the disturbed carbohydrate metabolism. Nissen and Spencer¹⁵ found that sugar tolerance tests showed abnormal results in 57 per cent of 222 patients with arthritis and that age, sex, blood

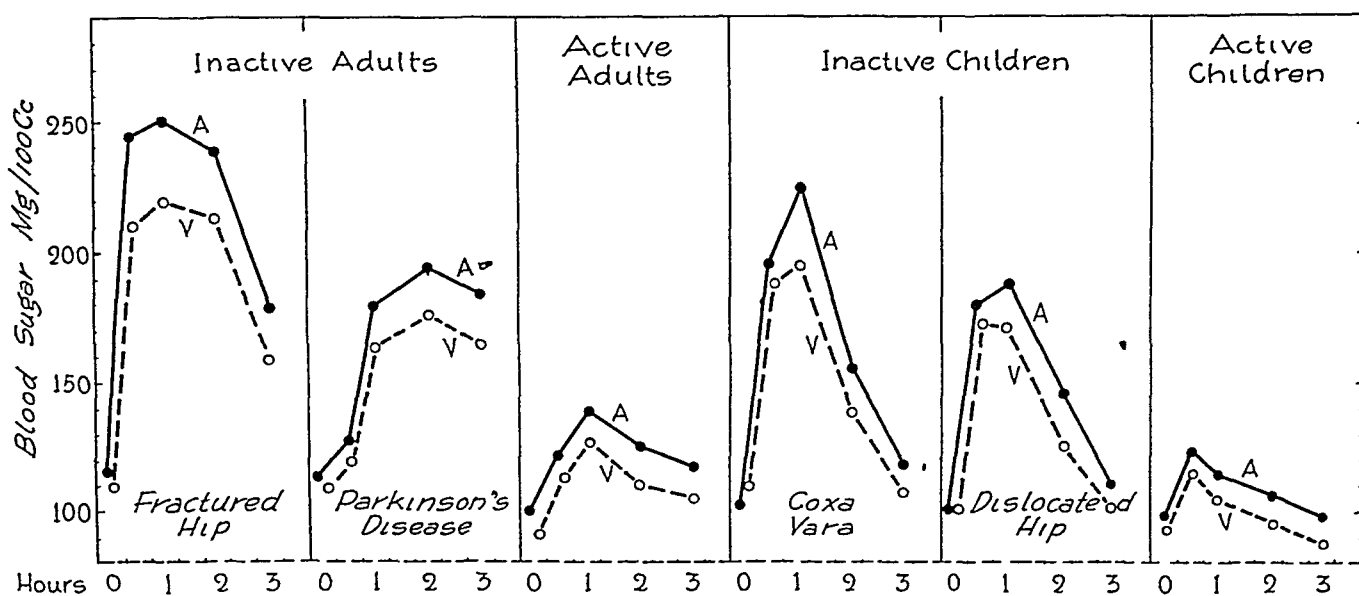


Chart 4—Illustrations of capillary-venous differences in sugar tolerance curves for 18 adults and 16 children confined to bed for long periods, compared with corresponding values for active adults and children. A, capillary blood, V, venous blood

they do when active. However, such a hypothesis can be questioned, because these patients do not eat as much as they do when active and consequently there is not as much available sugar to metabolize. Furthermore, the arteriovenous difference in the blood sugar curves after the ingestion of dextrose was found to be as great as or even greater than the normal difference. This suggests that the muscle of the inactive patient is capable of utilizing as much sugar as that of the normal person. It would appear that prolonged physical inactivity allows the pancreas to rest and results in sugar tolerance curves similar to those obtained when the pancreas is put at rest after insulin is administered in the treatment of nondiabetic malnutrition⁴ or when animals are placed on a high fat diet¹⁴. Under these conditions the pancreatic islets are relieved of the

pressure and focus of infection had no apparent relation to these results.

Diminished dextrose tolerance has been observed in certain patients with tuberculosis by Langston¹⁶ and by Kramer¹⁷. Rohdenburg, Bernhard and Krehbiel¹⁸ studied a variety of

14 Haist, R. E., Campbell, J., and Best, C. H. The Prevention of Diabetes, New England J Med **223** 607, 1940

15 Nissen, H. A., and Spencer, K. A. Sugar Tolerance in Arthritis, New England J Med **210** 13, 1934

16 Langston, W. Glucose Tolerance Test, J Lab & Clin Med **7** 293, 1922

17 Kramer, D. W. Glucose Tolerance Curves in Pulmonary Tuberculosis, J Lab & Clin Med **18** 1212, 1933

18 Rohdenburg, G. L., Bernhard, A., and Krehbiel, O. A Study of Sugar Mobilization Based upon Two Hundred and Twenty-Eight Human Cases, Am. J. M. Sc **159** 577, 1920

diseases, especially cancer,¹⁹ and found that many diseases are accompanied by hyperglycemia after ingestion of dextrose and that the concentration of the blood sugar is not the sole factor in the development of glycosuria. A reduction in sugar tolerance may occur in old age, according to Deren,²⁰ Hale-White and Payne²¹ and Marshall,²² especially in the presence of disease. I believe that the diminished sugar tolerance noted in old persons is due not to age but rather to the inactivity associated with age and that if these people were normally active their sugar tolerance would likely be normal. In this connection the effect of inactivity would vary with individuals.

A disturbed carbohydrate metabolism may be found in patients with mental disease in an institution, as shown by Robinson and Shelton,²³ who noted that this was common in 69 consecutive patients with nervous or mental disease. It would appear that inactivity is common to the patients with the diseases mentioned and that this factor may play an important role in the diminished carbohydrate metabolism.

SUMMARY

A study was made of the effect of prolonged physical inactivity on the dextrose tolerance of

19 Rohdenburg, G. L., Bernhard, A., and Krehbiel, O. Sugar Tolerance in Cancer, *J. A. M. A.* **72** 1528 (May 24) 1919.

20 Deren, M. D. Dextrose Tolerance in the Aged, *J. Lab. & Clin. Med.* **22** 1138, 1937.

21 Hale-White, R., and Payne, W. W. The Dextrose Tolerance Curve in Health, *Quart. J. Med.* **19** 393, 1926.

22 Marshall, F. W. The Sugar Content of the Blood in Elderly People, *Quart. J. Med.* **24** 257, 1931.

23 Robinson, G. W., Jr., and Shelton, P. Incidence and Interpretation of Diabetic-Like Dextrose Tolerance Curves in Nervous and Mental Patients, *J. A. M. A.* **114** 2279 (June 8) 1940.

86 nondiabetic patients—70 adults and 16 children—who had been confined to bed for one month to thirteen years by various pathologic conditions. A comparison was made between the dextrose tolerance of these patients and that of active adults and children.

It was found in general that the sugar tolerance was diminished in the patients who had been confined to bed for considerable periods. The fasting blood sugar in these cases ranged from 70 to 130 mg per hundred cubic centimeters, and the fasting urine was free from sugar. After the ingestion of dextrose the concentration of blood sugar rose to abnormal levels, the maximum being 364 mg, and varying amounts of sugar were found in the urine at various times. In many of the adults there was a high renal threshold for dextrose. In some patients who later became ambulatory for several months the sugar tolerance returned to normal. Age did not appear to have a definite relation to the diminished sugar tolerance. Hypertension, vascular disease, obesity and infection in themselves did not appear to be significant as causes.

The arteriovenous differences in the blood sugar of a group of inactive persons after the ingestion of dextrose ranged from 15 to 50 mg per hundred cubic centimeters, which is normal or greater than normal. These results indicate that the muscles of the physically inactive patients are capable of utilizing sugar normally.

It is suggested that during prolonged physical inactivity the pancreas is at rest because in this state there is not the demand for rapid storage and utilization of sugar that there is in active persons. Consequently, there may ensue diabetic-like reactions to dextrose tolerance tests even with normal fasting levels of blood sugar.

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ACUTE SUPPURATIVE BRONCHOPNEUMONIA

HAROLD NEUHOF, M D , AND ALEXANDER THOMAS, M D *

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The type of bronchopneumonia characterized by suppuration within the parenchyma has been known by various names. We shall employ the term "suppurative bronchopneumonia,"¹ which has been used for many years at the Mount Sinai Hospital. As evidence that pathologists have been long acquainted with the disease, Kaufmann's statement² that "pyogenic organisms may lead to suppuration, purulent liquefaction or abscess formation in the lung" may be quoted. It can also be assumed that clinicians know and recognize the disease. Nevertheless, suppurative bronchopneumonia under any name has been the subject of only few and fragmentary contributions³ by pathologists and clinicians alike. The subject, which has been under study by us for many years, is presented at this time because the current literature, which deals so fully with other forms of pneumonia, omits reference to it. The obvious possibilities in treatment with penicillin would appear to make imperative a more general recognition of the features of the disease.

The pertinent literature on the subject is so scanty that a brief survey will suffice. At the outset reference can be made to papers⁴ which deal chiefly with the differentiation between aerobic and anaerobic (putrid) pulmonary suppuration. There usually is omitted evidence to

suggest any relationship to a preexisting pneumonia, which may have been taken for granted. An indirect relationship to pulmonary suppuration is occasionally pointed out in instances of empyema in which bronchial fistulas are noted. Thus Hedblom⁵ referred to such empyemas as "presumably derived from small superficial abscesses" of the lung.

A feature of the literature which should be singled out for special mention is the bacteriologic aspect of bronchopneumonia. Two types of pyogenic pulmonary suppuration, the influenzal and that due to Friedländer's bacillus, have been thoroughly studied. Because of their distinctive characteristics, however, which are distinctly different from those which we shall describe, they will not receive further consideration in this paper. Staphylococcal suppurative pneumonia has been the subject of a number of contributions, particularly in recent years, the reports dealing for the most part with small groups of cases. The pediatric literature has been particularly concerned with staphylococcal pneumonia (Kanof, Kramer and Carnes,⁶ Gaspar,⁷ Clements and Weens⁸ and others). Neuhoef and Berck⁹ have called attention to the frequency of staphylococcal empyema in infants and young children. The impression that suppurative pneumonia is rare is to be noted also in the literature on the streptococcal pneumonias. Thus, Lawrence and Sutliff,¹⁰ in a review of cases of pneumonia in which hemolytic streptococci were found in the sputum, reported but 2 instances in which pulmonary suppuration due to that organism was found at postmortem ex-

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1 The disease is not given a distinctive listing in the *Quarterly Cumulative Index Medicus*. There are two forms of suppurative pneumonia, due respectively to the *Bacillus influenzae* and Friedländer's bacillus, which are listed but, as will be indicated, they will be omitted from consideration because of many different features which they possess.

2 Kaufmann, E. *Pathology for Students and Practitioners*, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 1, p. 400.

3 With the exception of the special variety of staphylococcal pneumonia, as will be noted.

4 (a) Eisendrath, D. N. *Surgery of Pulmonary Abscess, Gangrene and Bronchiectasis Following Pneumonia*, Philadelphia M. J. 8 786, 1901. (b) Sauerbruch, F. *Die Chirurgie der Brustorgane*, ed. 2, Berlin Julius Springer, 1920, vol. 1, p. 540. (c) Meyer, W. *Observations on Lung Suppuration and Its Treatment*, Arch. Surg. 6 361 (Jan., pt. 2) 1923. (d) Kline, B. S., and Berger, S. S. *Pulmonary Abscess and Pulmonary Gangrene*, Arch. Int. Med. 56 753 (Oct.) 1935.

5 Hedblom, C. A. *Pulmonary Suppuration*, M. Rec. 96 441, 1919.

6 Kanof, A., Kramer, B., and Carnes, M. *Staphylococcus Pneumonia*, J. Pediat. 14 712, 1939.

7 Gaspar, I. A. *A Study of Primary Staphylococcal Pneumonias*, New York State J. Med. 41 834, 1941.

8 Clements, H. H., and Weens, H. S. *Staphylococcal Pneumonia in Infants*, J. Pediat. 20 281, 1942.

9 Neuhoef, H., and Berck, M. *Staphylococcal Empyema and Pyopneumothorax: Pathogenesis, Pathology, Symptoms and Treatment*, Arch. Surg. 30 543 (March) 1935.

10 Lawrence, E. A., and Sutliff, W. D. *Streptococcus Pneumonia*, New York State J. Med. 40 1233, 1940.

amination In a series of 911 cases of pneumonia described by Cecil and Lawrence¹¹ only 3 per cent were reported to be due to hemolytic streptococci and no mention was made of any special characteristics of the streptococcic group The rarity of pulmonary suppuration as a complication of bronchopneumonia was referred to by Senerchia and Livengood¹² in their report of 8 cases of pneumonia in which *Streptococcus viridans* was cultured from the sputum There are scattered references to the occurrence of suppurative pneumonia ascribed to pneumococci

The pathologic features of suppurative bronchopneumonia are scarcely mentioned in textbooks that devote considerable space to other bronchopneumonias However, two unusual types have been described a putrid necrosis, first reported by Kessel,¹³ and a form of extreme necrosis of the lung (necrotizing pneumonia) reported by French authors¹⁴ In the former, pulmonary cavitation was discovered on routine roentgen examination—and such cavities were found to heal spontaneously within a short time—or was found as an incidental lesion at autopsy The microscopic study of autopsy material led to the belief that the lesion was of vascular origin, in the form of thrombosis in the pneumonic area followed by infarction and secondary necrosis The necrotic pneumonia of French authors has been reported as a rare lesion characterized by widespread destruction of pulmonary tissue Moolten¹⁵ described a fatal case and laid stress on the factor of necrosis

From the foregoing paragraphs it can be said that while suppurative pneumonia under various names has long been known to exist the disease has not been the subject of more than a fragmentary presentation Our survey of the pathogenesis, pathology, roentgen features, clinical manifestations and therapy is based on an analysis of 120 well documented cases which have been studied at the Mount Sinai Hospital over a period of more than ten years These cases do not comprise all the instances of suppurative pneumonia observed in that period Many cases of mild and of transient disease have been

omitted because they were not adequately proved or documented and because we wished to concentrate attention chiefly on the more distinctive cases

Special attention will be devoted to the clinical forms of the disease because its many variations comprise its most interesting as well as its most distinctive feature Roentgenograms will be employed to illustrate clinical forms as well as the evolution of the disease

The 120 cases which comprise our series were all cases of suppurative pneumonia due to aerobic pyogenic organisms The anaerobic infections of the lung (putrid pulmonary abscess) have no place in this paper They comprise a separate and unrelated entity, and their inclusion, except for considerations of differential diagnosis, would serve no useful purpose There will also be excluded all forms of suppurative pneumonia or pulmonary suppuration which can be regarded as secondary, such as suppuration secondary to bronchial neoplasm, tuberculosis or bronchiectasis The pulmonary suppurative foci which occur in septicemia are of a different as well as a specific nature and will therefore not be considered The reason for excluding pneumonias due to the Friedlaender or influenza organisms has already been stated

Clinical and roentgen features as well as data obtained at operation or at autopsy comprise the basis for study of the 120 cases Cultures of pus obtained under favorable conditions confirmed the diagnosis in many instances It can be stated at once that a variety of aerobic organisms were cultured We shall show that little if any difference could be ascertained in the pathologic conditions or in the clinical course in relation to the causative organism

INCIDENCE

In contradistinction to the statements in the literature on the subject, our evidence is that suppurative bronchopneumonia is not rare We have stated that the 120 cases of our series were gathered during a period of approximately ten years and that not a few cases of mild disease and incompletely documented cases were omitted We now realize also that in the earlier years, before the features of suppurative pneumonia were appreciated by us, a considerable number of cases were overlooked Thus suppurative bronchopneumonia should not be regarded as a rare disease

There appears to be a seasonal incidence of suppurative bronchopneumonia which corresponds generally to other varieties of pneumonia In our series the number of cases reached a peak in the beginning of December and extended

11 Cecil, R L, and Lawrence, E A Pneumonia in Private Practice, J A M A **111** 1889 (Nov 19) 1938

12 Senerchia, F F, Jr, and Livengood, H R Streptococcus Viridans Pneumonia, New York State J Med **41** 143, 1941

13 Kessel, L The Clinical Aspect of Aputrid Pulmonary Necrosis, Arch Int Med **45** 401 (March) 1930

14 Letulle, M, and Bezançon, F La pneumonie dissequante necrotique, Ann de med **12** 1, 1922

15 Moolten, S E Pulmonary Infection and Necrosis in Diabetes Mellitus, Arch Int Med **66** 561 (Sept) 1940

through March. It then tapered off to a low point in July, but cases were encountered throughout the year. In scarcely any of the cases was there a history suggesting epidemic features. Emphasis should be placed on the fact that the disease occurs as a rule in previously healthy persons. Thus many of the severe and fatal cases were encountered amongst such patients.

Cases of the disease appear to be about equally divided between the sexes. It is seen in all age groups, with a disproportionate preponderance

of suppurative pneumonia in infants⁹ and the frequency of the pneumococcic variety in young children. We assume that the disease is not uncommon as a terminal infection in old and debilitated or cachectic persons, but we can draw no conclusions from our limited experience with such cases.

PATHOGENESIS

The evidence in our series of cases justifies only an assumption that the pathogenesis of suppurative bronchopneumonia is similar to that

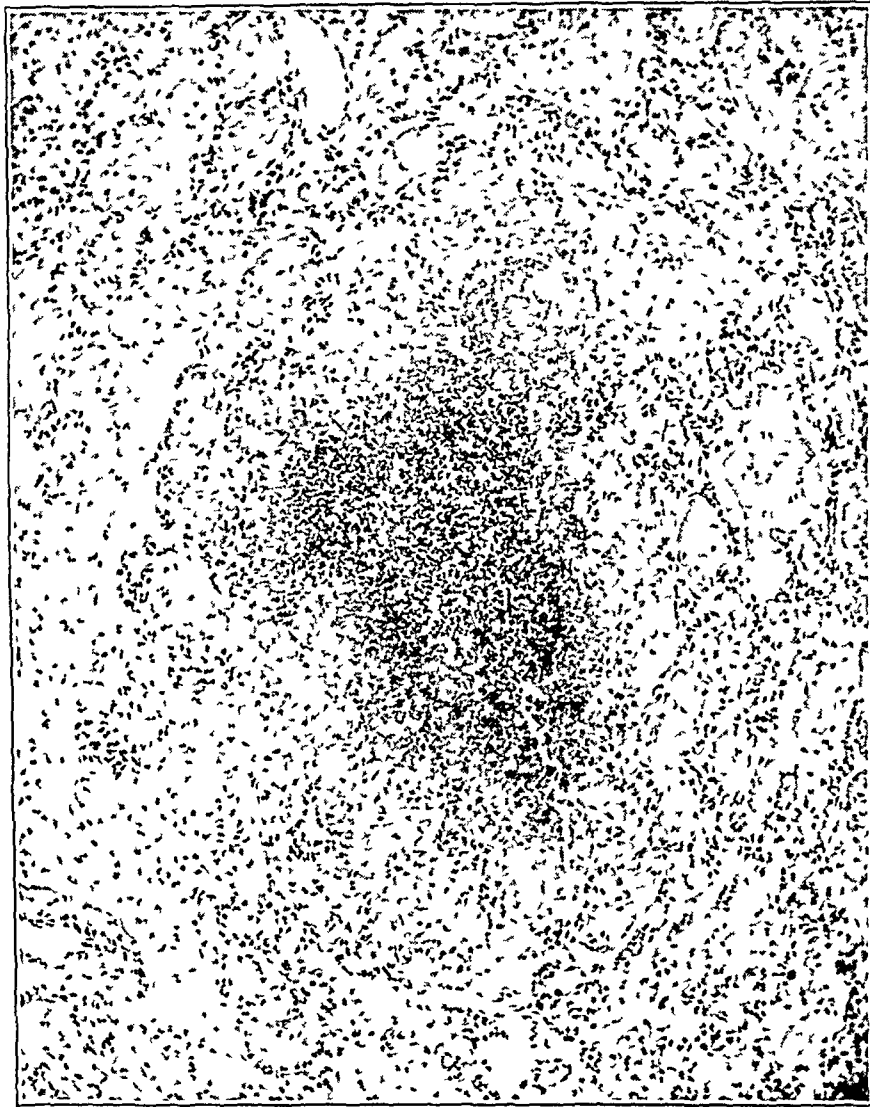


Fig 1—Necrosis in an area of suppurative bronchopneumonia

in children. One third of the patients were children under the age of 10 years (see the

Age Distribution

Age, Years	Cases
Under 1	10
1-9	30
10-19	10
20-29	18
30-39	15
40-49	15
50-59	9
60-69	11
70 and over	2

table). The disproportion may be accounted for by the high incidence of the staphylococcic va-

riety of suppurative pneumonias in infants⁹ and the frequency of the pneumococcic variety in young children. We assume that the disease is not uncommon as a terminal infection in old and debilitated or cachectic persons, but we can draw no conclusions from our limited experience with such cases. In a large percentage of the cases there was a history of an infection of the upper respiratory tract which immediately preceded the onset of the pulmonary disease. It will be pointed out shortly that the suppurative pneumonias involve bronchopulmonary segments as in bronchopneumonia. Thus a similar pathway of descending infection appears likely in suppurative bronchopneumonia. We stated that the disease usually is encountered in previously healthy persons. In a few cases the disease occurred in persons with diabetes, but there appeared to be no disproportionate increase in incidence, and the extent of the lesion

was not appreciably greater than that seen among normal persons

GENERAL AND CLINICAL PATHOLOGY

As in many other conditions, autopsy is likely to reveal chiefly the most advanced stages of the disease, and therefore reliance on autopsy alone may lead to false impressions. In our series of cases considerable knowledge of the gross pathologic changes was obtained at operation (for pulmonary abscess and for the pleural complications of suppurative pneumonia) and will be discussed under appropriate captions

purative process itself (fig 1). In several instances, there were, in addition, vascular lesions in the nature of acute nonspecific arteritis and thrombosis (fig 2). These were apparently the result of intense infection and led to further necrosis and suppuration secondary to anemic infarction.

There were identified roentgenologically, at operation and at autopsy, instances in which the degree of destruction of pulmonary tissue was outstanding. In some of these cases there were large cavities with limited surrounding inflammatory and suppurative zones. In others the

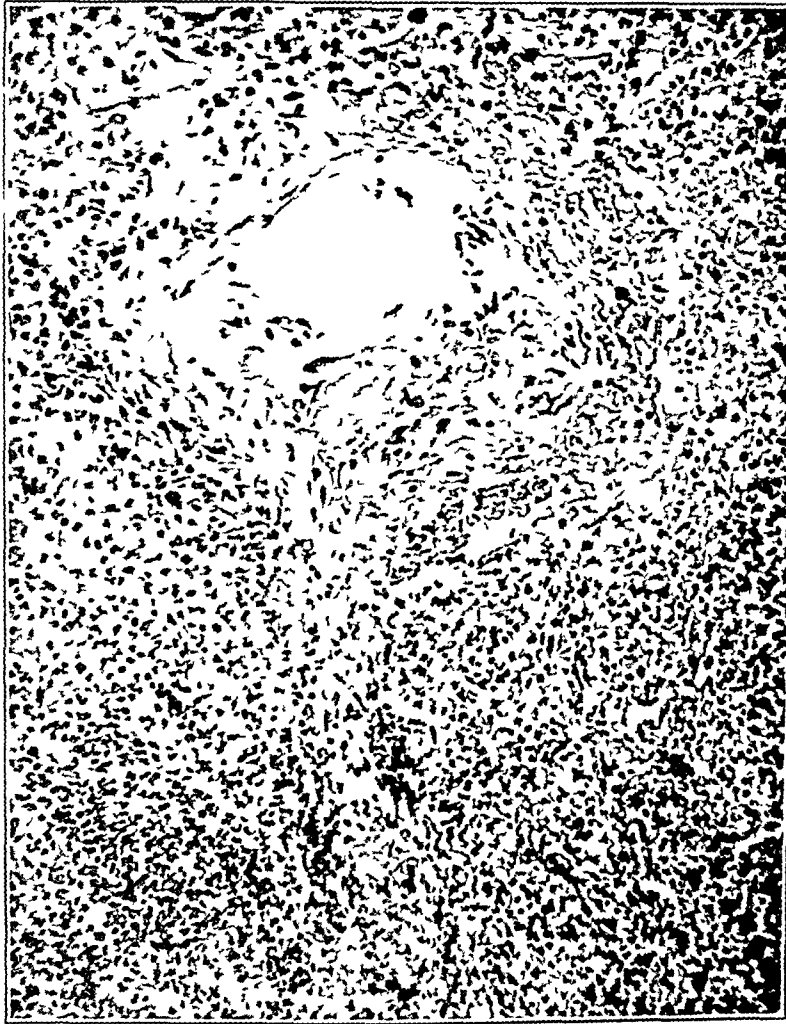


Fig 2—Suppurative bronchopneumonia with acute nonspecific arteritis and thrombosis

The pathologic conditions as noted at autopsy will be briefly considered. The lesions were often multiple. Each consisted of a severe bronchopneumonia with varying degrees of suppuration and necrosis. Single or multiple abscesses were usually present. It should be noted that the lesion or lesions were of substantial proportions, each involving much or all of one or more bronchopulmonary segments.¹⁶ Microscopic examination revealed that necrosis, which was almost invariably present, was due to the sup-

cavities contained small amounts of pus or necrotic tissue. To this distinctive and not rare type in which the element of necrosis is spectacular one of us (H N) has applied the term "necro-suppurative bronchopneumonia."

In view of the fact that suppurative bronchopneumonia is a lesion which occupies a bronchopulmonary segment,¹⁶ overlying pleuritis is of necessity a constant feature. In most of the cases the pleuritis is severe. Because the suppurative pulmonary lesion often extends to the surface of the segment or perforates into the pleural space, suppurative pleuritis is of frequent

¹⁶ Glass, A. Bronchopulmonary Segments, *Am J Roentgenol* 31: 328, 1934.

occurrence and is often found at autopsy. The pleural complications will be discussed in a consideration of the surgical aspects of the disease.

Suppurative bronchopneumonia can be defined as an infection in which either complete recovery or death usually occurs in the acute stage. Only infrequently does the lesion within the lung go on to a chronic phase with the formation of a chronic abscess or chronic interstitial pneumonia and bronchiectasis. Some of the characteristics of persistent or spreading suppurative bronchopneumonia which are of surgical interest because of complications will be subsequently discussed. Pulmonary abscess and suppurative pleuritis will be taken up in a consideration of the surgical aspects of the disease.

It should be pointed out here that the pathologic features of suppurative bronchopneumonia set the disease apart from putrid pulmonary infections. However, the two diseases appear to be confused at times according to the literature, and emphasis therefore should be placed on the differences which exist. Putrid pulmonary infections are almost always localized to one part of the lung, and thus are in striking contrast to suppurative pneumonia, which is often diffuse and situated in a number of segments. For example, suppurative pneumonia which has gone on to a nonputrid pulmonary abscess may be encountered in one part of the lung at the same time as areas of suppurative pneumonia in other parts. In other instances nonputrid pulmonary abscesses are present in several segments of one lung or in both lungs. Another distinguishing feature of the pathology is the extent of the pneumonitis which surrounds an existing pulmonary abscess. In the case of a putrid lesion the surrounding pneumonitis usually occupies a well defined and limited zone, whereas in suppurative pneumonia a collection of pus when present is often situated in the midst of an extensive pneumonic lesion. Only in those exceptional instances in which suppurative pneumonia goes on to typical abscess formation does the pathology resemble that of putrid pulmonary abscess. It is therefore incorrect to say that all cases of abscess of the lung belong in the same category and require the same treatment, regardless of whether the sputum has a foul or a non-foul odor and whether the infection is anaerobic or aerobic.

BACTERIOLOGY

The bacteriologic examinations in our series of cases were made from cultures of pus when pus was obtainable. The most reliable source of pus was operation, under which circumstances there was obviously the best chance for the disclosure of the causative organism. Occasionally pus was obtained directly from the pulmonary lesion.

Our remarks concerning the bacteriology of suppurative bronchopneumonia are based on cultures obtained from empyemas or from pulmonary abscesses and not from sputum. Anaerobic as well as aerobic cultures were taken. In the great preponderance of cases a single pyogenic organism was obtained in pure culture. In no instance was an anaerobic organism cultured. The organisms most frequently encountered in pure culture were *Staphylococcus aureus*, hemolytic streptococci and pneumococci (of various types). Of special interest is the isolation of *Streptococcus viridans* in pure culture in a number of cases. In view of the fact that this organism could not be regarded as a contaminant, its presence in pure culture warrants the assumption that it is the causative organism in not a small proportion of cases of suppurative bronchopneumonia. It can be added here that the clinical course of *Str. viridans* infections was not appreciably different from that of suppurative bronchopneumonia due to other aerobic organisms.

The reasons for our unwillingness to place reliance on cultures of sputum as a satisfactory means of determining the bacteriology of the pulmonary infection should be stated. In some instances the same organism as that which existed in the pulmonary or pleural lesion was found in the sputum. Occasionally the same organism was obtained in pure culture. In the preponderance of cases, however, cultures of sputum revealed not only mixed organisms but organisms different from those obtained from the pus in the lung or pleura. Furthermore, cultures of sputum taken at different times disclosed different organisms in some cases. Because of these observations we believe that positive statements concerning the bacterial causation of suppurative bronchopneumonia should not be made on the basis of cultures of the sputum.

ROENTGENOGRAPHIC FEATURES

There appear to be no reports in the literature concerning the roentgen features of suppurative bronchopneumonia other than those from the Mount Sinai Hospital group. Bizarre and surprising patterns in cases of pneumonia undoubtedly have been seen and variously interpreted by many, yet their relationship to suppurative bronchopneumonia has not been noted. A number of years ago one of us (H. N.) came to realize that certain patterns were characteristic of the disease. Distinctive and sequential films from many cases were collected. As a result of their study a single feature, the presence of one or more areas of rarefaction in the midst of pneumonic infiltration, was found to be roentgenologically pathognomonic. We have called

attention to this feature at various times. In 1938 we indicated its significance in relationship to suppurative bronchopneumonia and to aerobic pulmonary abscess.¹⁷ Sussman¹⁸ in 1940 referred to it in a consideration of the roentgen aspects of nonputrid pulmonary suppuration. The proportion of cases of suppurative bronchopneumonia in which characteristic areas of rarefaction will be revealed in roentgenograms cannot be stated. They are common in our series, which consists however of specially selected cases. As will be emphasized, they may also be revealed in laminagrams when not visible on ordinary roentgenograms.

In the absence of rarefaction there is no one pathognomonic roentgenologic sign of suppurative bronchopneumonia. However, there are a number of distinguishing features which are encountered so frequently that they can be regarded as characteristic of the disease. Rabin¹⁹ has called attention to these features in his division of the roentgen manifestations of suppurative bronchopneumonia into six varieties: (1) interstitial infiltrations about the bronchi, blood vessels and interlobular septums, (2) homogeneous densities, either single or multiple, of lobular, segmental or lobar distribution, (3) changes indicating the presence of focal, segmental or lobar atelectasis or emphysema, (4) multiple areas of rarefaction indicating the presence of a destructive process within the lung or bronchi, (5) single abscess cavities of varying size, and (6) collections of fluid and air within the pleural cavity which may obscure the intrapulmonary changes. It should be noted that these features may exist separately or in various combinations. Indeed, the possibilities of combinations either in the same pulmonary field or in different fields are almost endless. As has already been pointed out, spontaneous resolution and healing may occur in lesions in which, according to roentgenograms, there appears to be extensive destruction of pulmonary parenchyma.

Concerning atelectasis in pneumonia, with or without emphysema, bronchial obstruction is generally assumed to be the sole cause. As evidence in support of this view it can be said that atelectasis occurs more often in infants and young children, apparently because of an inability to expel tenacious bronchial exudate by coughing. Without entering into a discussion of this debat-

able subject, it can be pointed out that other causes for atelectasis have been postulated. In any event one may say that atelectasis as such should be regarded as only an incidental feature of the pathologic changes of suppurative bronchopneumonia.

Of special interest are the cases in which roentgenograms reveal large, so-called balloon cavities. Such thin-walled cavities may be found to persist in films after apparently complete subsidence of pulmonary infection. A mechanical factor which seems to be chiefly responsible for these balloon cavities has been described by Moolten.²⁰ Whether the mechanism is a ball valve action in a bronchus, centrifugal traction on the lung²⁰ or is differently conceived,²¹ the important points to note are that the lesion is not in the nature of extensive pulmonary destruction, that spontaneous disappearance is likely to occur and that there are no indications for surgical (or other) treatment. The roentgen and clinical differentiation of balloon cavities from pulmonary abscess complicating suppurative bronchopneumonia offers no difficulties.

Sectional roentgenography (laminagraphy) has been referred to in a foregoing paragraph as of value in revealing the existence of areas of rarefaction in the midst of apparently solid pneumonic infiltration. There were a few cases in this series in which the diagnosis of suppurative bronchopneumonia remained in doubt after the usual films were studied. In every instance laminagrams revealed the existence of areas of rarefaction. We do not know that laminagraphy would invariably disclose areas of rarefaction in cases of suppurative bronchopneumonia but have gained the impression that cavitation would be seen in at least the preponderance of cases of the severe type. Laminagraphy should therefore be employed when a definite diagnosis is required and the usual roentgenograms do not reveal areas of rarefaction in the midst of pneumonic infiltration.

SYMPTOMS AND PHYSICAL SIGNS

Suppurative bronchopneumonia can be defined symptomatically as an acute infection which is often preceded by an infection of the upper respiratory tract and which is characterized by fever, cough and the expectoration of purulent sputum. Thoracic pain occurs early in the course

17 Neuhof, H, and Touroff, A. S. W. Acute Aerobic (Nonputrid) Abscess of the Lungs, *Surgery* 4 728, 1938.

18 Sussman, M. The Roentgen Aspects of Non-Putrid Pulmonary Suppuration, *Am J Roentgenol* 44 345, 1940.

19 Rabin, C. B. Roentgen Features of Suppurative Bronchopneumonia, *J Mt Sinai Hosp* 8 32, 1941.

20 Moolten, S. E. Mechanical Production of Cavities in Isolated Lungs, *Arch Path* 19 825 (June) 1935.

21 Caffey, J. Regional Obstructive Pulmonary Emphysema in Infants and in Children, *Am J Dis Child* 60 586 (Sept) 1940.

of suppurative pneumonia and is sufficiently common to be regarded as a feature of the disease. It is of pleuritic character, usually sharp and localized, and occasionally so severe as to comprise the outstanding symptom. The variations of these typical clinical features are numerous and will be discussed later in some detail. Indeed, they must be known in order to recognize suppurative bronchopneumonia in all its protean forms.

Fever is usually moderate, at times on a high level, but may be irregular or even remittent. Emphasis should be placed on the fact that it may be mild and out of proportion to the extent and the intensity of the pneumonic lesion as revealed in roentgenograms. Indeed, there are instances in which the febrile course has largely subsided at a time when roentgenologic evidence of an extensive lesion still exists.

Except in infancy or early childhood expectoration of purulent sputum or of frank nonfetid pus occurs in almost all cases and should be regarded as the distinctive clinical feature of the disease. The amount of purulent sputum usually is substantial, a common daily range being from 1 to 6 ounces (30 to 180 cc) or even more. When scanty it consists of small quantities of thick, tenacious purulent sputum. Occasionally expectoration of pus may be scanty or absent at the outset, to become profuse later in the course of the disease. Signs of toxemia are seen within the first week in severe infections, and prostration often is extreme under such circumstances. When the disease is protracted, toxemia and expectoration are usually extreme. We wish to repeat, however, that the clinical course cannot be measured by the extent of the pulmonary lesions as revealed in roentgenograms.

Before discussing physical signs it should be noted that dyspnea is not a uniform feature of suppurative bronchopneumonia, even in its most acute form. Omitting a discussion of the factors which are generally responsible for it, it should be pointed out that in suppurative bronchopneumonia dyspnea is most commonly observed when pleural penetration or infection either is impending or has already taken place. There are no distinctive physical signs of suppurative bronchopneumonia. The signs are similar to those of other bronchopneumonic lesions. They often are scanty in comparison to the extent of the lesion as revealed by roentgenogram or at operation. Physical signs of cavitation should not be expected even when cavities are of substantial dimensions. On the other hand, suppurative pleuritis generally produces characteristic physical signs, particularly on percussion. Breath sounds become distant or absent in any gross

form of pleural invasion (generalized effusion, pneumothorax or pyopneumothorax).

Examination of the blood often reveals a moderate to severe leukocytosis, although a white cell count below 10,000 is not rare. Anemia is present in protracted infections, which are usually accompanied by pronounced toxemia.

DIFFERENTIAL DIAGNOSIS

Suppurative bronchopneumonia usually can be diagnosed readily on the basis of the clinical features alone. A knowledge of the many clinical varieties of the disease is necessary for its recognition. The roentgenographic features are characteristic in a substantial proportion of the cases. In doubtful instances laminagraphy may reveal areas of rarefaction and thereby clarify the diagnosis. However, a protracted clinical course may raise the question of the existence of some other disease. Thus, a course extending over several weeks may suggest pulmonary tuberculosis or neoplasm. Concerning the latter, bronchoscopy may prove to present positive evidence and should, therefore, not be omitted in doubtful cases. As to tuberculosis, it has been our experience that if the sputum is frankly purulent the absence of tubercle bacilli on several examinations precludes its existence. When the sputum is scanty, the examination of spreads of pus obtained by bronchoscopy may be required in order to establish the presence or absence of tuberculosis. In cases of shut-off putrid pulmonary abscess (which are exceptional) the sputum may be quite free from foul odor. The diagnosis may not be established until (1) fetid sputum appears, (2) foul pus or odor is revealed by bronchoscopy or (3) a putrid empyema establishes the diagnosis. The problem of roentgen differentiation of suppurative bronchopneumonia from forms of virus pneumonia has arisen. At first sight, mottled patches of bronchopneumonia with suggestive areas of rarefaction indicated the diagnosis of suppurative bronchopneumonia. However, the absence of purulent sputum combined with severe prostration, the leukopenia and the subsequent resolution (according to roentgenograms) of the lesion without the development of cavitation excluded the diagnosis of suppurative pneumonia. It is our belief that the simulation of cavitation on the roentgenogram is due to the pattern made by mottled patches of bronchopneumonia. Finally, mention should be made of unusual suppurative pulmonary lesions, such as actinomycosis, which may at times simulate suppurative bronchopneumonia so closely that the correct diagnosis can be established only after prolonged observation and study.

CLINICAL VARIETIES

The general description of the clinical manifestations of suppurative bronchopneumonia has been given. We wish to present here the clinical varieties which have been encountered. Since unusual manifestations which are of frequent occurrence really characterize the disease, the descriptions of the clinical varieties will be followed in each instance by one or more illustrative cases. A number of unusual or extreme examples have been purposely chosen. The 120 cases which comprise this series fall into four main groups but the classification is largely one of convenience and some measure of overlapping.

- II Secondary suppurative bronchopneumonia
 - A Postoperative
 - B In cachexia
 - C From other predisposing causes
- III Surgical forms
 - A Pulmonary abscess
 - B Empyema and pyopneumothorax
 - 1 With proved pulmonary focus
 - 2 Without proved pulmonary focus
- IV Complications of suppurative bronchopneumonia
 - A General
 - 1 Cerebral
 - 2 Septic
 - B Local
 - 1 Lattice lung
 - 2 Bronchiectasis
 - 3 Pericarditis
 - 4 Mediastinitis

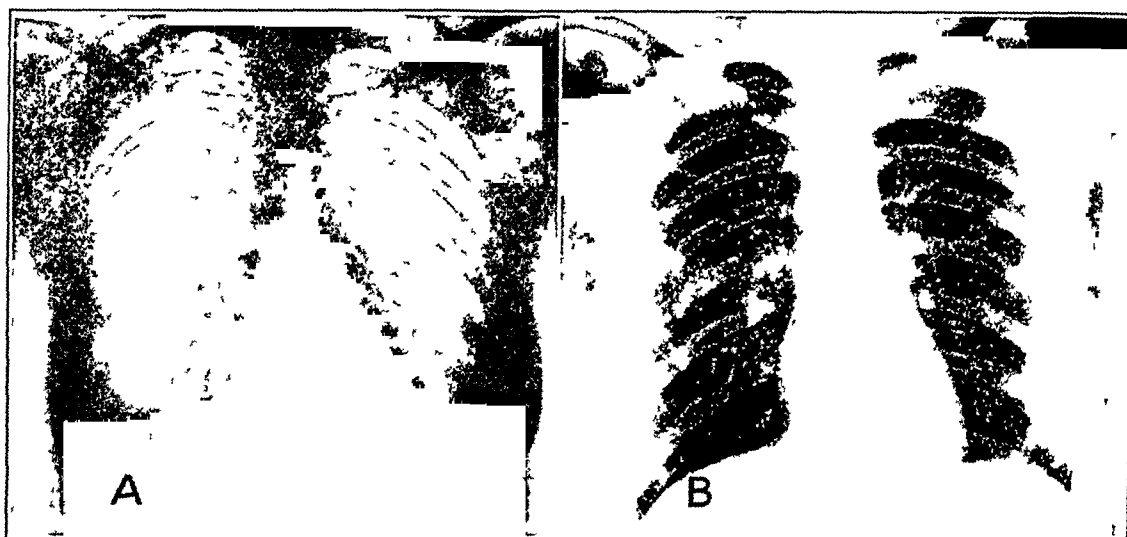


Fig 3 (case 1)—*A*, infiltration in the middle portion of the right pulmonary field, with cavitation and fluid level, *B*, eight days later, spontaneous resolution

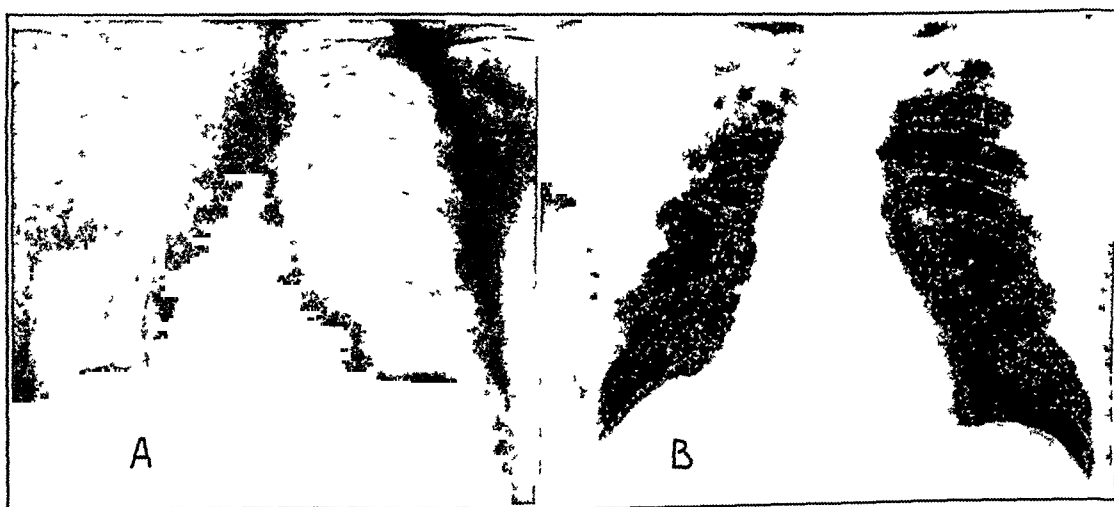


Fig 4 (case 2)—*A*, dense consolidation of the upper lobe of the right lung, with areas of rarefaction and fluid levels, *B*, eight weeks later, in process of resolution

will be noted. The complications are included in the classification because they comprise an important aspect of the disease.

CLASSIFICATION

- I Basic forms
 - A Localized suppurative bronchopneumonia
 - B Diffuse suppurative bronchopneumonia

IA Localized Suppurative Bronchopneumonia—This is the most common form in which the disease is manifested. The lesion occupies a more or less substantial portion of one or two adjacent bronchopulmonary segments, and the clinical course usually lacks surgical or other complicating features. In the following 3 illus-

trative cases the first was chosen as typical of the most benign form, and the second was selected because it was characterized by a severe and toxic course. The third is presented because there was a unique opportunity to observe the pathologic conditions of suppurative bronchopneumonia in a patient who recovered.

CASE 1—C A, a 25 year old woman, had a three week history of cough, pain in the right side of the chest, low fever and expectoration of thick greenish sputum. Roentgen examination showed infiltration in the axillary segment of the upper lobe of the right lung with a circular area of increased aeration, the second roentgenogram revealed a definite cavity with a small fluid level. The course was benign, there was low grade

should be placed on the fact that despite the pathologic alterations noted at operation healing occurred, with complete disappearance of all roentgen evidence of pulmonary infiltration.

I B Diffuse Suppurative Bronchopneumonia—This type is characterized clinically by a more severe or prolonged course. Fatal cases are encountered in this group. Clinically, the outstanding feature is profuse purulent expectoration in virtually all instances. Roentgenologically, the lesion differs from the preceding by a more widespread invasion with ill defined limits. There may be involvement of portions of the adjacent or the more remote lung which occurs often

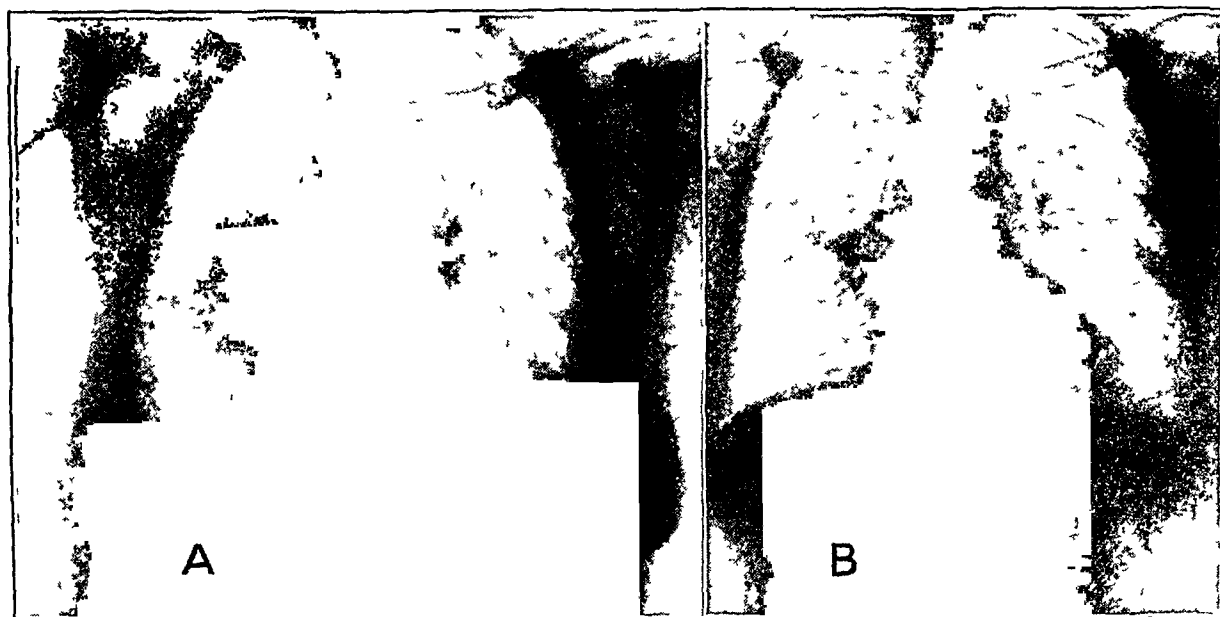


Fig 5 (case 3)—A, preoperative roentgenogram, showing dense infiltration of right lung with small irregular, faint areas of increased aeration, B, two weeks later, in process of resolution.

fever for three days, and the temperature was normal thereafter. Roentgenography showed progressive clearing. On follow-up examination the patient was entirely well, and the roentgenogram was normal.

CASE 2—J F, a 49 year old man, had a 4 week history of fever and cough which was productive of purulent sputum. A roentgenogram showed dense consolidation within the upper lobe of the right lung. There was a severe septic course for ten weeks, with local extension of pneumonitis and on the roentgenogram appearance of areas of rarefaction with fluid levels. He raised profuse purulent sputum throughout the course. Convalescence was gradual, with complete recovery and a negative roentgenogram. A bronchogram after recovery was negative.

CASE 3—G L, a 52 year old man with mild diabetes, was admitted to the hospital with a two week history of dyspnea, fever and cough, with scanty expectoration. Roentgen examination showed dense infiltration in the middle third of the right lung, with small irregular areas of increased aeration. Physical signs suggested empyema, and aspiration revealed pus. On the diagnosis of encapsulated empyema, thoracotomy was done. There were well defined pleural adhesions sealing off the free pleural space. The underlying lung was infiltrated, and wherever traversed by the aspirating needle small collections of pus were encountered. There was no single large collection of pus to be drained, and the exploration of the lung was discontinued. The clinical course apparently was uninfluenced by operation. Emphasis

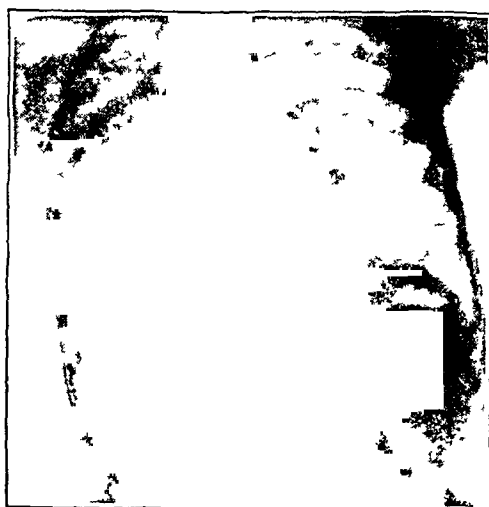


Fig 6 (case 4)—Diffuse pneumonic infiltration of most of the right lung, with numerous areas of rarefaction and exudate in the right pleura.

enough to be regarded as distinctive. Three illustrative cases will be presented. A case of its occurrence in a child, a case of its occurrence in an adult, and a fatal case.

CASE 4—L A, a 4 year old boy, presented a history of cough and fever for eight days. Diffuse pneumonic

infiltration of most of the right lung with numerous small areas of rarefaction was found on roentgen examination. The clinical course was extraordinarily mild, with slight fever for several weeks and expectoration of moderate quantities of purulent sputum. Successive roentgenograms in the hospital revealed increase in the areas of rarefaction, some with fluid levels, and an exudate in the right pleura. Progressive absorption and finally disappearance of all areas of pneumonic infiltration and rarefaction occurred. The final roentgenogram was normal. Follow-up for several years showed that the boy was entirely well.

CASE 5—S L, a 37 year old man, presented a four week history of moderate fever, cough and expectoration of small amounts of purulent sputum. A roentgenogram revealed infiltration in the midportions of both lungs, with a number of cavities, some with fluid levels. Numerous examinations of sputum did not show acid-fast bacilli. There was gradual improvement with normal temperature after three weeks. The final roentgenogram was normal.

CASE 6—N T, a 45 year old man, entered the hospital with a six day history of fever, pain in the left

logic features so closely resemble or are perhaps identical with those of the type under consideration. Cases are frequently encountered and are well known in surgical services. In our series of 120 cases only 5 cases of severe postoperative suppurative bronchopneumonia are included, making a disproportionately small number in relation to the whole. One illustrative case will be cited.

CASE 7—On B D, a 65 year old man, a subtotal gastrectomy for carcinoma of the stomach had been performed. Onset of fever occurred twelve hours postoperatively. Moderate fever continued thereafter, with purulent sputum, dyspnea and cyanosis. Death occurred on the ninth postoperative day. At autopsy diffuse necrotizing suppurative bronchopneumonia, with several areas of subpleural abscess formation, and diffuse purulent bronchiolitis were found.

III A Pulmonary Abscess—As has already been indicated, this lesion should be regarded as



Fig 7 (case 5)—A, bilateral infiltration, with a number of cavities resembling tuberculosis, B, four weeks later, resolution

side of the chest, cough, and expectoration of purulent sputum. On admission, there were signs of pneumonia over the upper lobe of the left lung. There was a progressive downhill course with spread of the pneumonia to the lower lobe of the left lung and the entire middle lobe of the right lung, development of cardiac irregularities and pericardial friction rub ending in death. Autopsy revealed confluent suppurative bronchopneumonia of the lower and upper lobes of the left and of the middle lobe of the right lung and acute serofibrinous pericarditis.

II A Postoperative (Secondary) Suppurative Bronchopneumonia—Since we are concerned with suppurative bronchopneumonia without obvious cause ("primary suppurative bronchopneumonia," for want of a better designation) cases of suppurative bronchopneumonia which occur postoperatively or in cachexia or which are of other more or less obvious cause do not belong here, strictly speaking. However, postoperative suppurative bronchopneumonia, in particular, warrants some consideration because the patho-

an infrequent complication of suppurative or necrosuppurative bronchopneumonia. It has been fully described elsewhere.¹⁷ The frequent occurrence of more or less localized collections of pus in suppurative bronchopneumonia may be mentioned. However, it is only when a stage is reached in which collections of pus are no longer merely incidental to the surrounding suppurative bronchopneumonia that a pulmonary abscess can be said to exist. In typical cases the abscess is solitary, of substantial proportions, situated superficially within the lung and overlain by agglutinating visceroparietal pleural adhesions. It contains a varying amount of pus and presents the orifices of one or more bronchi. A case will be presented which is of particular interest because the complete evolution of the disease is visible in the roentgenograms.

CASE 8—B R, a 54 year old man, was admitted to the hospital with an eight day history of fever and slight

cough. A roentgenogram showed pneumonic segmental infiltration in the upper lobe of the left lung. An irregular febrile course followed. After several days expectoration of purulent sputum began, and it later became more profuse. There was no response to chemotherapy. Successive roentgenograms showed development of a fluid level in the lesion and progressive localization with abscess formation. After five weeks in the hospital the abscess was drained through sealing off adhesions in one stage. On culture of pus from the abscess *Streptococcus intermedius* was isolated. The postoperative course was characterized by prompt subsidence of the fever, cough and expectoration, and progressive healing of the cavity and wound. Follow-up examination showed the patient to be entirely well. Roentgenographic examination revealed slight residual fibrosis, and a bronchogram was normal.

pleural lesion. In the case of anaerobic (putrid) infections of the lung, the tendency to localization of the pleural infection is pronounced. The causative lesion in the lung is a more or less obvious perforated pulmonary abscess. Hence pyopneumothorax is the rule. In cases of suppurative bronchopneumonia the tendency to localization often is slight, especially in children. Thus, in not a few of the cases of its occurrence in children the disease is characterized by a diffuse subtotal or even total empyema. The extent of the air component is unpredictable. Thus, there are instances in which the pyopneumo-

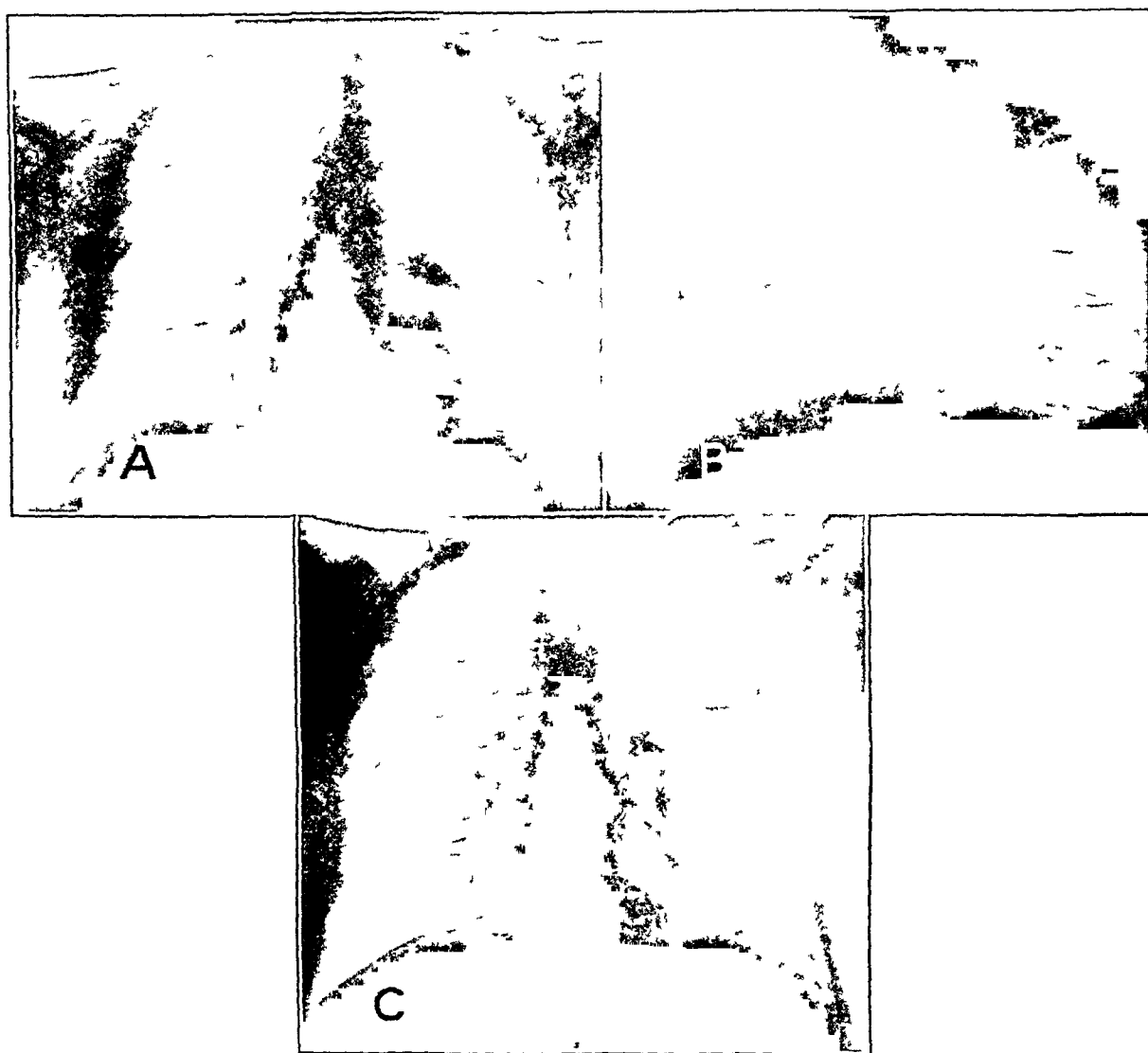


Fig 8 (case 8)—*A*, pneumonic infiltration in the middle of the left pulmonary field, *B*, (lateral projection) beginning cavitation on the same date, *C*, one month later, just before operation, showing localization of the lesion with development of a pulmonary abscess.

III B Empyema and Pyopneumothorax—As a complication of suppurative bronchopneumonia of any variety pleural invasion may exist in the form of a localized or diffuse collection of pus, and the empyema may or may not contain air. Indeed, there are cases of bilateral empyema in our series in which one side contained air and the other side did not, and cases of multiple empyema over one lung with the same differences. Many factors lead to the varying characteristics of the

thorax is obvious and extreme even in young children or infants, whereas in other cases little or no air is present.

The chief purpose of the foregoing discussion is to stress an important fact which warrants general recognition. In some cases in which the empyema at first contains no air according to roentgenograms reexamination later discloses the presence of a pyopneumothorax. In other cases operation for airless empyema may disclose an

obviously ruptured abscess of the lung. The reason for the absence of air under such circumstances is of interest. We believe that the perforated focus is compressed by the accumulation of fluid in the pleura and is thus incapable of supplying enough air from its communicating bronchus to be visualized in a film. Thus we have seen instances in which at open operation for encapsulated, non-air-containing empyema there was the orifice of a perforated pulmonary abscess with a blowing bronchial fistula immediately following the evacuation of pus. It was evident that the latter permitted the bronchial communication to open up and that the compression of the empyema previously prevented the escape of air. In other cases it may be postulated that the pulmonary abscess cavity becomes collapsed (or even healed) by the mechanism of a perforation fol-

Two illustrative cases will be presented, 1 of empyema with a proved perforated pulmonary focus and the other a case of pyopneumothorax without such a proved focus.

CASE 9—A M., a 53 year old man, entered the hospital with a three day history of severe bronchopneumonia of the lower lobe of the right and of the left lung. There was a stormy course for several weeks, with development of roentgen evidence of a right pleural effusion, followed by evidence of an encapsulated right paravertebral empyema. Thoracotomy was performed and a localized empyema with a ruptured large pulmonary abscess and a bronchial fistula in the floor of the empyema cavity when pus was removed were found. The opening of the pulmonary abscess was enlarged and the empyema drained in one stage. Culture of pus yielded a pneumococcus of type IV. Recovery was rapid and complete.

CASE 10—J G., a 4 year old boy, had a ten day history of infection of the upper respiratory tract and fever. Signs of pneumonia of the middle and lower lobes of the right lung were observed on admission.

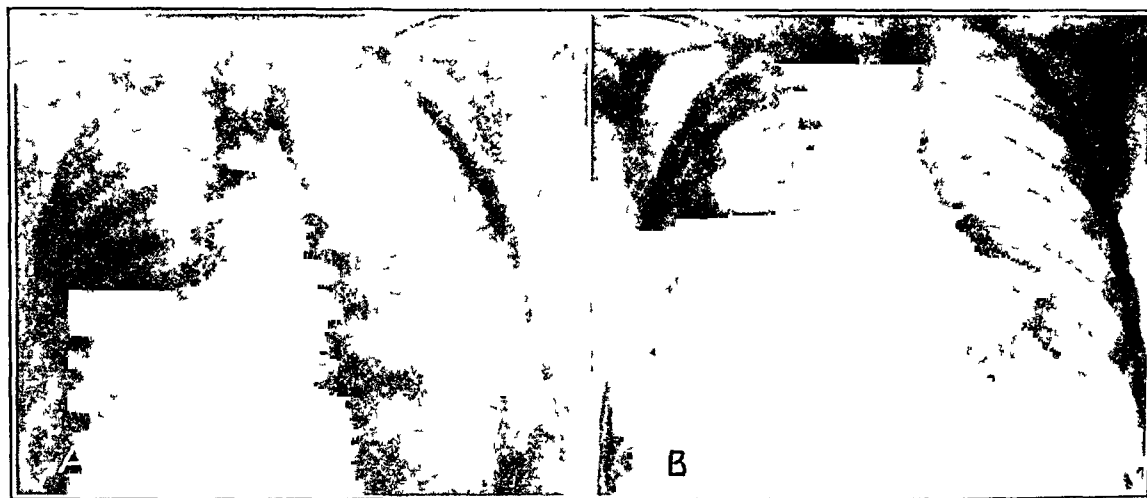


Fig 9 (case 10)—A, diffuse pneumonic infiltration of the right lung after two weeks of hospitalization, B, six days later, pyopneumothorax.

lowed by the pressure of intrapleural fluid and air. Indeed, we have encountered more than one large pyopneumothorax in which at the time of operation or subsequently the causative pulmonary focus was not demonstrated. Lastly, it can be assumed that at the time of a minor operation (closed drainage) the evacuation of an empyema may release the pressure on a collapsed perforated abscess and thereby open up a bronchial communication which did not exist theretofore. Thus, we have seen instances in which closed drainage of an empyema was accompanied by under water escape of several ounces of pus without air, to be followed by the bubbling of large quantities of air. The proof that an empyema was derived from a perforated pulmonary focus was lacking in only a small proportion of our cases. In these instances there may be postulated a small, so-called cortical pulmonary abscess or seepage from the underlying inflamed lung, as in lobar pneumonia.

After three weeks in the hospital physical signs of a large pyopneumothorax became evident and were confirmed by roentgen examination. An emergency stab thoracotomy and under water drainage of pus and air, followed several days later by open thoracotomy and drainage, was performed. At operation no bronchial fistula or pulmonary abscess could be demonstrated. Culture of pus revealed a pneumococcus of type I. There was rapid recovery, and on follow-up the roentgenogram was normal.

IV A General Complications of Suppurative Bronchopneumonia—Of the general complications, which are varied, we have selected two groups because of their gravity.

1 Cerebral. Evidence of cerebral infection existed in a number of the cases of severe or fatal disease. There were symptoms and signs of a cerebral abscess in 4. In all, the disease was fatal, and all terminated with suppurative meningitis. The focal signs of involvement of the brain were not typical, and precise localization of the lesion was not possible. In contrast to cerebral

abscesses of other origin, it may be said of this group that the cerebral lesion was invariably unfavorable for surgical drainage. Only in 1 instance did the pulmonary lesion appear to be undergoing retrogression at the time of the onset of symptoms referable to the complicating cerebral abscess. The report of this case follows.

CASE 11—S A, a 36 year old man, had been subjected to thyroidectomy for diffuse toxic goiter three weeks earlier at another hospital. Operation was followed by cough and fever, and there was increase in fever and onset of pain in the lower left part of the chest on the day before his admission to this hospital. Roentgen examination showed pneumonic infiltration of the lower lobe of the left lung, with abscess formation and empyema. Operation consisted of thoracotomy and drainage of two perforated pulmonary abscesses with encapsulated empyema. Culture of pus revealed *Str. viridans*. Postoperatively the pulmonary status improved gradually. The onset of tetany was controlled by specific therapy. Signs of cerebral abscess were

the following case an unusual picture appears to conform with this concept.

CASE 12—C C, a 2 year old girl had a two week history of infection of the upper respiratory tract and fever. She was admitted to the hospital acutely ill with high fever. The roentgenogram showed a large pulmonary abscess with a fluid level in the lower lobe of the right lung. Culture of blood yielded 60 colonies of *Staph. aureus* per cubic centimeter of blood. Operation, performed on the day after admission, consisted of a one stage pneumonotomy and drainage of a large abscess of the lower lobe of the right lung, the appearance of early lattice lung was noted. Later drainage of many superficial abscesses due to *Staph. aureus* was performed. The residual pulmonary activity was closed with a fat graft. Follow-up showed complete recovery.

IV B Local Complications of Suppurative Bronchopneumonia—Local complications are those which occur within or adjacent to the lung during the time of the disease or after it has run its acute course.

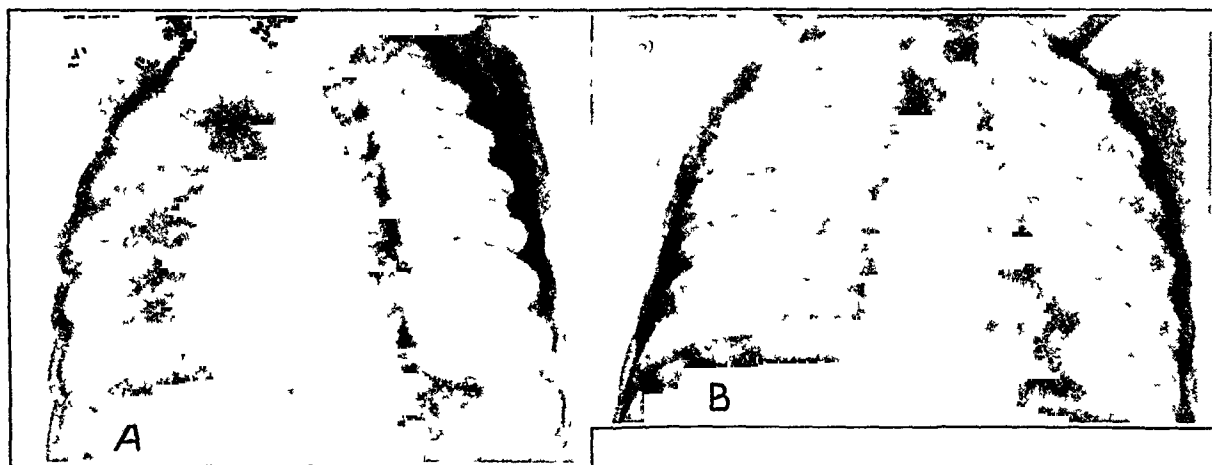


Fig 10 (case 12)—A, large pulmonary abscess of the lower lobe of the right lung on admission, B, follow-up roentgenogram after closure of the residual cavity with a fat graft (the patient completely well)

observed one week postoperatively, and lumbar puncture provided evidence of purulent meningitis.

2 *Septic* It has already been pointed out that metastatic abscesses of the lung occur as part of the picture of septicemia. In a sense these pulmonary foci may be regarded as foci of suppurative pneumonia. However, as has been indicated, the clinical and focal features are different from those of the latter disease, and embolic pulmonary abscesses, which have not been included in this paper, should not be confused with multiple areas of suppurative bronchopneumonia.

Septic foci derived from suppurative bronchopneumonia are rarely seen, although the suppurative focus in the lung can be logically regarded as a potential source of septic invasion of the blood stream. The direct source can be visualized as a suppurative phlebitis or arteritis in the midst of an area of suppurative bronchopneumonia (fig 2). Thus, multiple abscesses either in the pulmonary circuit or in the systemic system may be derived from such vascular sources. In

1 *Lattice lung* Lattice lung, generally regarded as a sequel of bronchopneumonia, has been found by us to be present during the acute phase. This fact not only is of importance clinically but is of interest to students of the disease because it establishes clearly the occasionally destructive nature of the lesion which warrants the term "necrosuppurative bronchopneumonia." We have seen two or more bronchopulmonary segments occupied by lattice lung with its many bronchial openings as early as two or three weeks after the onset of the pulmonary infection. Attention should be directed to the disproportion which may exist at times between a large area of lattice lung and the actual extent of destruction of pulmonary tissue. Mechanical forces, especially eccentric traction, may play so great a role that a given area of lattice lung appears to represent a much larger area of loss of pulmonary tissue than subsequently proves to be true. Two cases will be presented in order to depict the acute

and the chronic phase of lattice lung and their management

CASE 13—I H, an 11 month old boy, was admitted to the hospital with a history of five days of fever, cough and signs of pneumonia of the upper part of the right lung. A roentgenogram after one week revealed a shadow in the right upper part of the chest with three fluid levels. Thoracotomy was performed, and a large multiloculated perforated pulmonary abscess with extensive destruction of the upper lobe of the right lung and lattice lung were found. On culture of pus a pneumococcus of undetermined type was isolated. Post-operatively there was progressive improvement, and the large residual pulmonary cavity was closed with a fat graft. During the follow-up period of five years the wound healed, the boy became free of symptoms and roentgenograms have been normal.

CASE 14—R B, a 5 year old boy was admitted to the hospital with a history of pneumonia followed by

noted by bronchography a transient bronchiectasis as a complication of the acute phase. The bronchographic demonstration of restitution to normal without any residue of bronchial dilatation is of particular interest. It is safe to say that bronchiectasis as a complication is much more common in infants and young children than in adults. Of the illustrative cases of its occurrence in young patients, 1 was chosen for its demonstration of the reversibility of bronchiectasis and the other because of the evolution of bronchiectasis in a mild form.

CASE 15—L S, a 16 year old boy, had a three week history of fever and expectoration of thick odorless sputum. Pneumonic infiltration of the lower lobes of both lungs and a suggestion of a fluid level in the lower

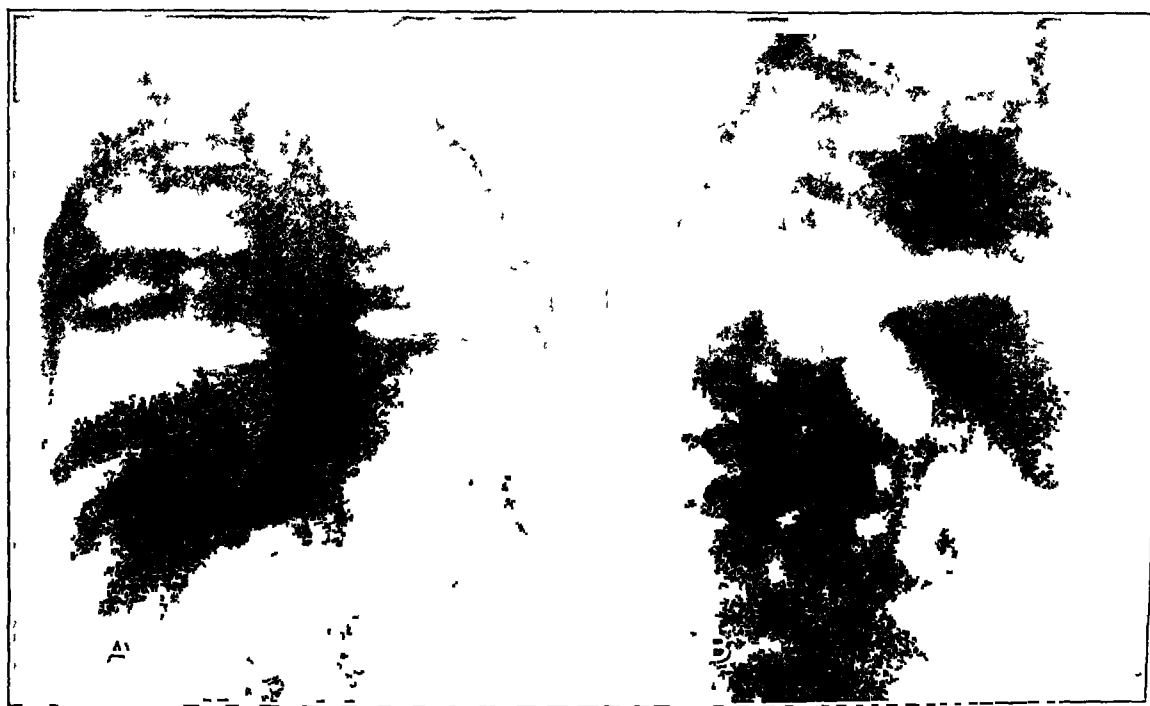


Fig 11 (case 13)—A, extensive lesion of the upper lobe of the right lung, with three large fluid levels, B, lateral view, showing great extent of the lesion

empyema one and one-half years before admission, treated by repeated aspirations of pus. Roentgen examination showed a right pyopneumothorax. At operation the right lung was found collapsed, and there was a large excavation in the lower lobe with numerous blowing bronchial fistulas. Culture of pus yielded a pneumococcus of type X. Several operations were performed in the next three years, chiefly thoracoplasties. Finally lobectomy, partly successful, was followed by fat graft for the closure of the remaining portion of lattice lung. Since then the patient has been well, with a healed wound but severe scoliosis. Recently the wound reopened, with the appearance of a small bronchial fistula.

2 Bronchiectasis The subject of bronchiectasis as a complication or sequel of suppurative bronchopneumonia is a large one but will be only briefly considered. There has been little opportunity to observe the actual development of bronchiectasis in association with suppurative bronchopneumonia. In some instances we have

lobe of the right lung were observed on roentgen examination. Bronchoscopic examination showed pus in the bronchi of both lower lobes. There was a gradual improvement, the fever and expectoration subsiding after one week in the hospital. A bronchogram after subsidence of the fever revealed dilatation of the bronchi of the lower lobe of the right lung, with abrupt ending of some third degree bronchi in globular dilatations. On follow-up the patient was entirely well. A bronchogram after two months showed persistence of bronchial dilatations, one year later, the bronchogram was normal.

CASE 16—C E, a 14 year old girl, had a three week history of fever, pain in the left side of the chest and mucoid expectoration. The roentgenogram on admission showed pneumonia of the posterolateral portion of the lower lobe of the left lung and another, ten days later, showed atelectatic pneumonia of the same segment. The fever subsided after a few days, and expectoration became profuse and purulent. A bronchogram after four weeks showed bronchiectasis of the lower lobe of the left lung, with shrinkage of the lobe. Pneumothorax therapy was followed by cessation

of cough and expectoration. Pneumothorax was discontinued after one year. The patient has been well since then, with normal roentgenograms after several years.

3 **Pericarditis.** Suppurative pericarditis is the third local complication for consideration and occurs as a result of direct extension from the adjacent area of suppurative bronchopneumonia. Theoretically, therefore, this variety of suppurative pericarditis should be regarded as amenable to surgical relief, in contrast to suppurative pericarditis of metastatic origin. However, the infection within the pericardium is so insidious and in some respects so incidental to severe suppurative bronchopneumonia that the diagnosis is not often made, and when it is made, the lesion is rarely amenable to surgical relief. It is found not infrequently at autopsy. In our series there was 1 clinical case of suppurative pericarditis



Fig 12 (case 14)—Chronic right pyopneumothorax with collapsed lung

complicating bilateral suppurative bronchopneumonia and empyema. Cure followed drainage of the pericardium.

4 **Mediastinitis.** Suppurative mediastinitis occurs occasionally as the result of direct extension from areas of suppuration within the lung and pleura. In our series it was noted as an invasion of the posterior mediastinum in fatal cases and was apparently incidental and without clinical manifestations. Suppurative mediastinal lymphadenitis was also noted occasionally at autopsy in cases of widespread suppurative bronchopneumonia.

TREATMENT

Brief consideration of the treatment of suppurative bronchopneumonia will suffice at this time because the disease is to be regarded as self-

limited, essentially unaffected by treatment and going on to recovery, death or surgical complications. There has been ample opportunity to employ chemotherapy, including the newer sulfonamide drugs, in our series of cases, and the results have been disappointing. Indeed, a response to treatment which could be regarded as definite or decisive was seen so rarely that we are in considerable doubt as to the advisability of employing chemotherapy. At most its use for only a few days appears warranted, to be discontinued if the clinical and roentgen picture of continuing suppuration in the lung is noted.

Concerning serum therapy for the pneumococcal variety of suppurative bronchopneumonia, definite results were not noted. Thus, the statement made concerning the use of the sulfonamide drugs appears to apply with at least equal force to serum therapy.

In contrast to the foregoing methods, supportive medical treatment has undoubtedly been of value in aiding in the recovery of a substantial proportion of the patients with severe suppurative bronchopneumonia. Rest in bed, maintenance of nutrition, administration of oxygen and liberal transfusions of blood have been factors which appeared not only to aid in increasing resistance but actually to facilitate recovery. Persistence in vigorous supportive therapy is indicated, particularly when the course is protracted, because recoveries which may not be anticipated will at times result.

PRINCIPLES OF SURGICAL MANAGEMENT OF PULMONARY AND OF PLEURAL COMPLICATIONS

Although characterized by suppuration, the disease does not often require surgical intervention so far as suppuration within the lung is concerned. Single or multiple suppurative foci of even large size may undergo spontaneous recession by drainage via the bronchi. By way of contrast, surgical intervention is frequently indicated for anaerobic infections of the lung (putrid pulmonary abscess) according to the views which we have maintained.²² In various parts of this paper the pathologic and the clinical and roentgenologic manifestations of surgical complications of suppurative bronchopneumonia have been described. We wish to discuss here the principles of operative treatment of the complications in the lung and pleura.

Pulmonary abscess can be termed an unusual complication. Suppuration within the parenchyma

²² Neuhof, H., and Touroff, A. S. W. Acute Putrid Abscess of the Lung. *Principles of Operative Treatment, Surg., Gynec. & Obst.* 63: 353, 1936.

ma is, of course, part of the disease, and coalescence of several adjacent purulent foci is undoubtedly of common occurrence. In a paper dealing with aerobic pulmonary abscess,¹⁷ we classified the pulmonary suppurative lesions of the type of pneumonia under discussion into three groups: (1) pulmonary abscess in the midst of, and apparently an incidental part of, an extensive necrosuppurative bronchopneumonia, (2) pulmonary abscess as the prominent or predominant

may lead to spread of the infection. Suppuration in the midst of pneumonic infiltration may eventually lead to typical abscess formation, but this evolution must be awaited for days or even weeks before one proceeds with operation. The evolution of such an abscess and its management is illustrated by case 8 and its accompanying roentgenograms. Roentgenograms are seen to provide the only guide to indicate the existence of a pulmonary abscess because the transition of

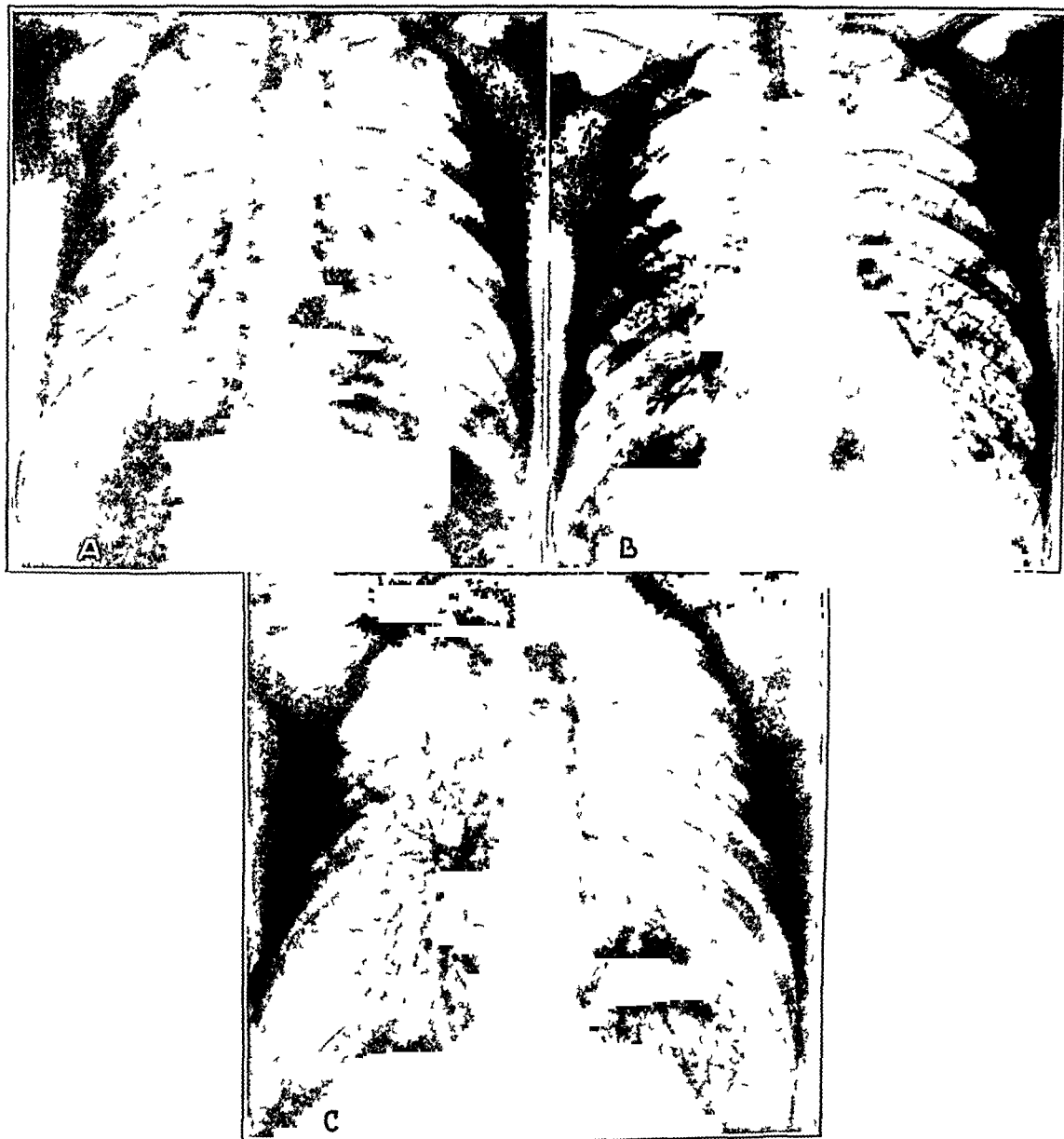


Fig 13 (case 15)—*A*, infiltration of the lower lobe of the right lung, with suggestive areas of rarefaction, *B*, nine days later, bronchial dilatation and sacculation of bronchi of the lower lobe of the right lung, *C*, one year later, normal bronchogram

ing lesion but surrounded by a considerable area of necrosuppurative bronchopneumonia, (3) typical pulmonary abscess with a more or less sharply limited and narrow surrounding zone of infected lung. Our purpose in calling attention to this classification is to emphasize that surgical intervention is indicated only for the typical pulmonary abscess. Operative treatment employed for the other varieties not only is of no value but

symptoms from suppurative bronchopneumonia to abscess is too slight for clinical identification. In a study of the films special search should be made for additional pneumonic areas in the same or in the opposite lung, because the knowledge of the existence of such areas may lead to withholding operation even in cases of typical pulmonary abscess. In any event, a knowledge of their existence is essential in the decision as to

operation and in interpretation in the event of an unsatisfactory postoperative course

The operative treatment of the pulmonary abscess must be based on precise roentgen localization of the abscess. If there is any doubt as to the site of contact of the abscess with the thoracic parietes the spot localization method of Rabin²³ should be employed. In the appropriate section of this paper a pulmonary abscess was described as solitary, of substantial proportions, superficially situated within a pulmonary lobe and sealed off from the free pleura by visceroparietal agglutinating adhesions. Emphasis should be placed here on the necessity for traversing these adhesions in the one stage operation which we advocate. On the one hand, infection of the free pleura is a grave complication, on the other hand, the interference with coughing and expectoration which goes with a two stage operation will almost certainly lead to serious spread of the infection within the lung. But the most important objection to a one stage operation is the

problem exists. We have discussed this problem elsewhere²⁴ as well as the technic of operation for pulmonary abscesses in usual situations.

Whereas pulmonary abscess comprises a complication of suppurative bronchopneumonia which permits of deliberate study, pleural complications require at times prompt surgical intervention. Thus it can be mentioned that (chiefly in infants and young children) an abrupt pleural invasion by rupture of a pulmonary abscess into the free pleural space produces a situation in which immediate surgical intervention (closed drainage) may be imperative in order to save life. The organism most often encountered in such cases in infants and young children is *Staph aureus*. Indeed, these staphylococcal pneumonias are generally regarded as highly fatal, yet not a few patients can be saved by prompt recognition of the pleural complication and equally prompt surgical intervention.

The possible sources of a suppurative pleuritis are to be noted in the diagram which has been

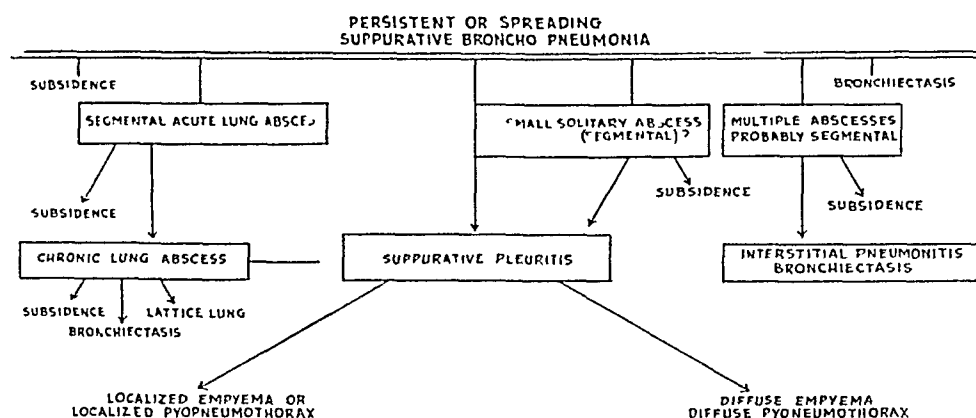


Fig 14—Surgical aspects of suppurative bronchopneumonia

danger of infection of the pleura, hence the necessity for careful localization of the abscess followed by an exact one stage operation. The principle of the operation should consist of the entry into the abscess through its most superficial portion, where the shell of lung is thin, compressed and avascular, and the excision of the thin shell within the limits of pleural adhesions. Expectoration of quantities of pus, which characterizes the preoperative course, should subside promptly after a satisfactory operation. Reference should be made to the rare situation of an abscess facing a fissure, the diaphragm or the mediastinum. In such circumstances the abscess, although always situated superficially in the pulmonary lobe, may excite only local adhesions. Thus agglutinating visceroparietal adhesions may be absent, and a special surgical

devised to indicate the surgical aspects of suppurative bronchopneumonia (fig 14). The caption "Persistent or Spreading Suppurative Bronchopneumonia" is employed to indicate that the surgical (particularly the pleural) complications are derived usually from a persistence of or spread from the original focus. As can be seen from the diagram, suppurative pleuritis may be evolved directly by extension from the pulmonary focus or may be secondary to a segmental perforated acute abscess at the site of suppurative bronchopneumonia. It may also be secondary to smaller solitary suppurative foci or to one of a series of multiple pulmonary abscesses. In rare instances it is a complication of a subacute or a chronic pulmonary abscess. In any event, the evolution of the pleural lesion may be gradual, resulting in a well localized empyema. This slow evolution is characterized by relatively mild manifestations, by physical signs suggesting

23 Rabin, C. B. Precise Localization of Pulmonary Abscess, The "Spot" Method, *J Thoracic Surg* 10 662, 1941

24 Footnotes 17 and 22

pleural fluid and roentgenologically by the evidence of a localized pleural effusion. If the purulent effusion invades a region remote from the thoracic parietes, such as the paravertebral, interlobar or intrapulmonary areas, the evolution of the empyema may be obscured by adjacent "sympathetic" effusions of serous character situated in the parietes. It should be emphasized, however, that such effusions may reveal pyogenic organisms on culture. The localized collection of pus in the pleura may contain air or may be full of fluid. In the former case the evidence of communication with the bronchus is, of course, clear. The question of air-containing and non-air-containing empyemas was taken up in the section (III B) dealing with empyema and pyopneumothorax. From the viewpoint of surgical therapy the important fact is that a perforated pulmonary abscess often is the underlying cause, whether or not the empyema contains air.

The operative treatment of encapsulated empyema is thoracotomy and drainage. In the case of an empyema complicating suppurative bronchopneumonia emphasis should be placed on the frequency with which two or more encapsulations exist. Thus, identification and interrelation must be determined before operation by a study of roentgenograms taken in various positions. The encapsulations are usually intercommunicating, at times via a narrow neck. Occasionally, however, they are separate, in which circumstances they are derived from separate foci of suppurative bronchopneumonia. In several cases in our series they were bilateral. The basic principle of the operative treatment of encapsulated empyema is adequate drainage of every collection of pus. This often implies drainage to the site of the perforated pulmonary focus. At times the orifice of the latter must be enlarged for better drainage of the pulmonary abscess into the empyema space.

Concerning the principles of surgical treatment of diffuse empyema or pyopneumothorax, reference has already been made to imperative closed drainage for effusions under tension, most frequently occurring in infants and young children. There are two important facts to be emphasized: first, that such effusions with or without air are common and can be fatal in a short time if not definitively released; and, second, that they may occur abruptly and unexpectedly at an early stage (in time) of the pulmonary infection. Of course recovery will not occur merely because of timely and adequate treatment of such pleural effusions. In some of our cases the suppurative disease in the lung proved to be too extensive (as ascertained by autopsy) for a significant re-

sult to be anticipated. However, appropriate surgical treatment should be instituted regardless of the known or the assumed severity of the pulmonary lesion, for unexpected recoveries following drainage have occurred in our cases.

In view of a conflicting literature we wish to place emphasis on our view that closed drainage is the only treatment for a rapid accumulation of pus and air or of pus alone in the free pleural space in cases of suppurative bronchopneumonia. It is the safest if not the sole means of influencing definitely not only the displacement of the heart and mediastinum but the infection in the pleural space. The clinical picture with which one may be faced can be restated. The patient, usually an infant or child, acutely ill with the manifestations of bronchopneumonia, becomes more acutely ill, often with dramatic and ominous suddenness. Cyanosis and dyspnea if already present become much more pronounced. The pulse races and becomes smaller. The heart is shifted toward the opposite side, there are the physical signs of fluid or of air and fluid, and in any event respiratory sounds are absent on the affected side. If a roentgenogram is taken it will reveal a shift of the heart, usually more pronounced than anticipated. Thus, there rarely is any doubt as to the diagnosis. To temporize with Potain aspiration on the assumption that the infection in the lung is too acute or the patient is too ill for the extremely simple operation of closed drainage may remove the only chance for recovery. We believe that the arguments which have been advanced elsewhere²⁵ in favor of closed drainage as against repeated aspiration apply with particular force to the situation under discussion.

Closed drainage may prove to be the sole procedure required for the treatment of the pleural complication. In most instances, however, open drainage, often carried to the site of a perforated pulmonary focus, will be required after the acute manifestations have subsided and the general condition is satisfactory. Occasionally pulmonary cavitation with its bronchial fistulas will persist after thoracotomy if the destructive lesion was extensive. This creates a special problem which we have usually solved by the simple expedient of free grafting of fat.²⁶ The latter procedure has also been employed in the acute stage in those rare instances in which dangerously large quantities of air escaping in the closed drainage system jeopardize the life of the patient.

25 Neuhof, H., and Hirschfeld, S. Suppurative Pleuritis in Children. Its Pathogenesis, Diagnosis and Treatment, *Am J Dis Child* **44** 973 (Nov) 1932.

26 Neuhof, H. Free Transplantation of Fat for Bronchopulmonary Cavity, *Ann Surg* **113** 153, 1941.

PROGNOSIS

In the discussion of incidence we pointed out that the group of 120 cases on which this report is based was exceptional in the sense that it comprises only adequately proved and well documented cases and in large part of severe disease. Thus, the mortality of 24.2 per cent (29 deaths) in this series is unquestionably much too high for the disease as a whole, as is to be noted in the following brief statement concerning the causes of death in the 29 cases. Four occurred among cachectic persons or after major operations, in 5 instances death took place within a few days of the patient's admission to the hospital, in 4 fatal cases there was evidence of metastatic cerebral abscess. In most of the surgical cases, death was referable to the persistence or the spread of the disease within the lung.

In the section dealing with surgical aspects of suppurative bronchopneumonia we dealt with the subject of aerobic pulmonary abscess in which the differentiation was made from more or less localized suppuration in the midst of suppurative bronchopneumonia. Operation has been performed erroneously on the latter lesion with unsatisfactory or even fatal sequelae. On the other hand emphasis should be placed on the excellent results of drainage operations for true pulmonary abscess. With precise roentgen localization a one stage operation performed through substantial pleural adhesions has resulted in cure in all the cases (15) in this series.

SUMMARY AND CONCLUSIONS

Suppurative bronchopneumonia, a descriptive term for an acute infection of the lung which has been long known under various names, is not rare and yet it is the subject of only a fragmentary literature. A systematic presentation of the subject has been attempted on the basis of a study of 120 well documented cases. The effort to include only proved cases resulted in a collection which contains a disproportionately high percentage of cases of severe forms of the disease.

The seasonal incidence of suppurative bronchopneumonia corresponds apparently with that of other forms of bronchopneumonia. As a rule the disease occurs in otherwise healthy persons. It apparently has a higher incidence in children than in adults.

Since the disease presents the features of an infection of the upper respiratory tract descending into bronchopulmonary segments, the pathogenesis of suppurative bronchopneumonia appears

to be identical with that of nonsuppurative aspiration bronchopneumonia.

The pathologic features consist of a severe bronchopneumonia involving one, several or many portions of the lung or lungs. Substantial portions of bronchopulmonary segments are involved. Spread from primary areas appears to be chiefly by the mechanism of spillover. Varying degrees of suppuration and necrosis occur within the affected segments of lung, usually with the formation of single or multiple foci of liquefaction within areas of bronchopneumonia. Necrosis is at times outstanding and spectacular. The term "necrosuppurative bronchopneumonia" appears appropriate under such circumstances. The microscopic feature of suppurative bronchopneumonia is a combination of suppuration and necrosis in varying degree. In addition there is seen at times a nonspecific arteritis with thrombosis.

Suppurative pleuritis is a common complication. It may be circumscribed or diffuse, an empyema or a pyopneumothorax.

A true pulmonary abscess, a substantial collection of pus surrounded by a limited zone of pneumonitis, is an infrequent complication as compared with suppuration in the midst of a pneumonic area. A true abscess is situated superficially within a pulmonary lobe with overlying agglutinating visceroparietal adhesions. Adhesions are local and may not be visceroparietal when an abscess occupies one of the specified rare sites.

There is no distinctive bacteriologic agent for suppurative bronchopneumonia. One or more of the aerobic pyogenic organisms, most commonly *Staph. aureus*, hemolytic streptococci and pneumococci, are encountered. A pure culture of a single organism is the rule. *Str. viridans* is encountered as the sole organism in a substantial proportion of the cases. There appear to be no distinctive features of suppurative bronchopneumonia which can be related to the infecting organism, although it should be noted that the staphylococcic variety occurs characteristically in infants and young children. The only reliable cultures are those of material obtained by aspiration through the thorax or at operation. Cultures of sputum have proved to be unreliable in determining the causative organism.

The roentgen features are extremely varied and often bizarre. The six main types which are set forth may exist singly or in various combinations. One or more areas of rarefaction in the midst of pneumonic infiltration comprise the characteristic feature. This roentgen evidence of

suppurative bronchopneumonia, which can be regarded as pathognomonic, is not seen in all cases. It may be revealed by laminagrams when not visible in ordinary films.

The essential symptoms are initial thoracic pain which is at times severe, cough, expectoration of substantial quantities of purulent sputum (in adults) and fever. The physical signs are not distinctive.

The clinical forms of suppurative bronchopneumonia are varied, and a knowledge of the variations is required in order to recognize the disease in one of the protean forms in which it is manifested. The forms are somewhat arbitrarily classified under four headings: basic, secondary, surgical and general and local complications.

When suppurative bronchopneumonia pursues a prolonged course differentiation must be made from other causes of pulmonary suppuration, notably tuberculosis, neoplasm, fungous infection and even putrid pulmonary abscess.

Suppurative bronchopneumonia, including the necrosuppurative variety, is a self-limited disease which is not materially influenced by any of the currently employed sulfonamide compounds or by serum therapy (in the group of cases due to pneumococci). The treatment is primarily supportive and when vigorously pursued may greatly facilitate recovery.

Surgical complications within the thorax are common, comprise an important aspect of the disease and will be recognized promptly if the suppurative nature of the disease is kept in mind. Pulmonary abscess is an unusual complication. A one stage operation was followed by recovery in all cases.

The mortality in the reported series of 120 cases was high because of the inclusion of a disproportionately high percentage of cases of severe forms of the disease. The mortality of suppurative bronchopneumonia is due in large part to intrathoracic complications.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1944

NEUROSIS AND THE WAR

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The time has not yet come when one can thoroughly discuss the psychiatric problems of World War II, but the subject is so important that a preliminary review is worth while. The data are accumulating all too rapidly and many papers have been written, but most of the more important observations are in publications still "restricted" by the military authorities. The American papers available deal largely with induction centers, training camps and morale. Interesting as these may be, they do not attack the crux of the situation, the acute nervous breakdown of the soldier in combat. The English literature has more papers about the acute psychiatric disorders of battle. The survivors from Dunkirk provided a rich material¹ and since then the aviators², but even these papers do not provide answers to the fundamental questions, which will be available only when more facts are accumulated and a more mature tolerance smoothes out the polemic tendency of some writers to support one or another of the "schools" of psychiatric thought.

A paper by Grinker and Spiegel³ has been released in Solomons and Yakovlev's "Manual of Military Neuropsychiatry," which gives one the most up-to-date picture of psychiatric treatment in the zone of combat. There is also a short paper by Grinker in *The Journal of the American Medical Association*⁴. The picture is vivid and terrible, a gross caricature of the reactions seen in civil life. As one would expect, the fear reactions are the commonest. Among many variations, three types of severe anxiety states may be picked out. There is that of the patient who is brought into the hospital shaking and looking terrified, his pulse is rapid and his blood pressure high, he sweats, has wide palpebral fissures and dilated pupils. There are

coarse tremors, and speech is often a pathetic stutter. Startle reaction is marked, and attacks of laughing and crying, or of dashing about, may occur. Another clinical picture is that of somatic disintegration, in which the patient's condition may simulate Parkinson's syndrome or catatonic dementia precox because of the peculiar postures and motor disturbances. The face may be mask-like and the limbs rigid and tremulous while the patient stands semifixed, sometimes with the hands below the knees, the gait may show propulsion. He may drool saliva, hold food for a long time in his mouth and have only gurgles and giggles for language. The behavior is childish and fearful and seems to represent a regression from adult integration.

A third type of severe anxiety state, less dramatic but more common, is stupor, in which the patient lies in bed staring vacantly. Many patients recover rapidly without treatment, passing through a stage of mutism to stammering speech and then fairly normal behavior with gaps in the memory. When a patient tries to overcome the amnesia, headache, dizziness and symptoms of anxiety may appear.

Milder anxiety states are more common than these three and are more like what one has seen in civilian life, with tremor, weakness, palpitation and fuguelike states in which the patients may wander away and be lost. They are tense and restless and sleep badly, often experiencing terror in battle dreams. After a few days they become quieter and then may insist that they can go back to their units, but a sudden noise will precipitate their symptoms all over again.

The cases of visceral expression of anxiety are abundant. Gastrointestinal symptoms predominate, such as anorexia, pain, belching and diarrhea. Enuresis is common. The "effort syndrome" ("soldier's heart"), so common in the last war, has been seen infrequently by these authors. Hysteria with conversion symptoms is rare. The patients observed have had the usual monoplegias, hemiplegias, pains and anesthetics, along with the typical indifference to their symptoms that sometimes caused medical officers to diagnose them as malingerers.

1 Sargant, W. W., and Slater, E. Acute War Neuroses, *Lancet* 2 1, 1940

2 Murray, J. Psychiatric Aspects of Aviation Medicine, *Psychiatry* 7 1, 1944

3 Grinker, R. R., and Spiegel, J. P. Management of Neuropsychiatric Casualties in the Zone of Combat, in Solomon, H., and Yakovlev, P. I. *Manual of Military Psychiatry*, Philadelphia, W. B. Saunders Company, 1944, chap. 35

4 Grinker, R. R. Treatment of War Neuroses, *J. A. M. A.* 126 142 (Sept 16) 1944

Treatment of the patients suffering from these disorders depends, first of all, on good diagnosis. Inexperienced officers have frequently mistaken the more severe reactions for schizophrenia and looked on them as hopeless. Early recognition and sorting out are essential. The patients must be divided into (1) those to be kept in the forward zones and returned to combat and (2) those that must go back to the general hospital. If exhaustion, hunger and thirst are important factors, quick sedation and rest with warmth, comfort and food will do much. Add to this encouragement and making much of the ideal of getting back to one's unit, and many of the patients are able to return to the front in a few days. When the anxiety is more severe the patient will not respond to this simple treatment and will have to go to the rear for exploratory therapy. The story of how sedative drugs may be used to make accessible repressed memories is one of the most interesting chapters in the medical history of this war. Of course it is not new, Lindemann⁵ wrote about it in 1930, and others since then have tried out the method in civil practice and found it only moderately useful. Various drugs have been employed and especially useful have been sodium amytal, sodium pentobarbital, sodium evipal, pentothal sodium and hyoscine hydrobromide. The one most used just now is pentothal (sodium ethyl-[1 methylbutyl]-thiobarbiturate). The method is variously known as "narcosynthesis," "narcoanalysis" and "hypnonarcoanalysis." The description of the treatment as given by Grinker and Spiegel is so good that I quote

The patient is isolated in a semidarkened room and is told that he is going to receive an injection which will make him sleepy. The drug is then injected in the antecubital vein at a slow rate (0.1 gm per minute) while the patient is asked to count backwards from the number 100. Shortly after the counting becomes confused and before actual sleep is produced, the injection is discontinued. If the patient is mute or stuporous and, therefore, cannot count, a corresponding depth of narcosis must be estimated from the tonus of the eyelids and the pupillary reflexes. In rare instances the injection is difficult because of violent tremor of the arm. In almost every case there is some increase in the symptoms of anxiety as the injection is initiated. As it proceeds, however, the tremors disappear, and the patient becomes quiet.

The patient is told in a matter-of-fact manner that he is on the battlefield, in the front lines. Depending upon the amount of known history, specific details are added corresponding to the actual situation at the time of the trauma. The amount of such stimulation which is necessary to start the patient talking varies tremendously. Some react with the first few words and launch into a vivid account of the action. Others resist

for varying periods, and when such resistance is maintained, the stimulation is made more dramatic and realistic. The therapist plays the role of a fellow soldier, calling out to the patient, in an alarmed voice, to duck as the shells come over, or asking him to help with a wounded comrade. Persistence is rewarded in almost every case by an account of the scene in progress.

It is impossible to describe the varied reactions during a pentothal narcosynthesis. Some patients act out the traumatic parts of the battle scene. If this is their reaction, they are allowed to get out of bed and to wander about the room looking for a slit trench, a lost friend, the Command Post, or whatever the piece of action in hand calls for. Some live through the scene verbally and emotionally without the production of much motor activity. They talk to unseen buddies, wince at unheard explosions, bury their heads under the pillow when the shells come close and flatten themselves out on the bed as if they were in the bottom of their foxhole.

It is electrifying to watch the terror exhibited in the moments of supreme danger such as at the imminent explosion of shells, the death of a friend before the patient's eyes, or the absence of cover under a heavy dive-bombing attack. The body becomes increasingly tense and rigid, the eyes widen, and the pupils dilate, while the skin becomes covered with perspiration. The hands move about convulsively, seeking a weapon, or a friend to share the danger. Breathing becomes incredibly rapid and shallow. The intensity of the emotion sometimes becomes more than the patient can bear and frequently at the height of the reaction, there is a collapse and the patient falls back in bed and remains quiet for a few minutes usually to resume the story at a more neutral point.

Other patients in whom there has been amnesia without much overt anxiety become suddenly blocked in the account of their experience as they approach the moment of trauma. As the anxiety begins to appear in anticipation of the traumatic scene, they cease talking and resume their characteristic defenses, they don't know what happened next. At this point the therapist applies pressure, demanding and forcing the patient to proceed. More than one session of narcosynthesis may be necessary to uncover the trauma.

During the time that the patient is thus wrestling with his traumatic experiences, the therapist plays an active or passive role in the performance to the degree required by the situation. No attempt is made to produce a hypnotic situation. The therapist remains as a vague background figure from which vantage point he can step into other roles as it becomes necessary. Some patients, especially those with only mild anxiety, good personality, and good contact with reality, are aware of the Medical Officer's presence throughout the treatment. They realize that they are telling the story to him and rely upon him only for emotion. In a severe case, however, in which there is much "living through" of the experience in the present tense, the patient is actually plunged in the battle situation. Here the Medical Officer is called upon to play a variety of roles. When the patient becomes convulsed with the violence of the terror, he must step in as a protective and supporting figure, comforting and reassuring the patient, and encouraging him to proceed.

When the initial problem is one of overcoming a somatic symptom such as mutism, deafness, or paralysis, the therapist may be required to adopt an authoritative role and command the patient to talk, to hear, or to move his limbs. Such direct interference is not always necessary. As the anxiety related to the traumatic situation emerges the symptom disappears spontaneously. A

⁵ Lindemann, E. Psychopathological Effect of Sodium Amytal, *Proc Soc Exper Biol & Med* 28: 864, 1931.

patient with a severe conversion symptom, under pentothal may begin to talk about his experiences in a calm, detached manner, but as he progresses, increasing quantities of anxiety are liberated. The somatic symptom disappears as the appropriate emotional reactions are liberated.

After this active therapy is finished psychotherapy by interview is kept up until the patient is fit for return to limited duty. Few of the patients who are sent back to general hospitals ever return to their units and the front lines.

Although I admire this paper by Grinker and Spiegel, so much that I review it at length and quote from it extensively, I do not agree with all the statements and implications. They state emphatically and without reservation that "*war neuroses are caused by war*, any one, no matter how strong or stable, may develop a war neurosis under proper circumstances." This assertion is apparently made in order to rid the psychiatrists of the subversive idea that war neurosis may be a breakdown based on "constitution or previous or latent neurosis." If they believed this they would "have a pessimistic therapeutic attitude," and "the quicker psychiatrists relinquish this idea the sooner they will achieve therapeutic success." On the same page the authors say that "the psychoneurotics crack up under mild battle stimuli."

Other writers on war neurosis do not agree with Grinker and Spiegel, for example, Sargant⁶ says that the war has forced on him the recognition of the constitutional nature of much war neurosis, and Henderson and Moore⁷ believe that war neurosis was "made in America" and predetermined before the man entered the service. I believe that some constitutional weakness and some tendency to neurosis are almost universal. It is a matter of degree and type of weakness that determines whether a man can stand much or little battle stress. Of course, it is desirable to get rid of the harmful, moralizing attitude that men who break with psychoneurotic symptoms are "weaklings." Grinker and Spiegel are probably right in saying that the terrors of modern war may break the best of us. I merely insist that the "best of us" have constitutional inadequacies and neurotic possibilities, and that recognizing this fact need not make the physician pessimistic about success in therapy.

This brings up the fact that there is no good and acceptable definition of "neurosis"—for the simple reason that no one knows what neurosis

is. Grinker and Spiegel take war neurosis "in simple terms" to be "the effect of an interaction between the dynamic forces of anxiety and the protective devices of the ego." Translated into American, this means to me merely that a man uses the sum total of his personality to combat fear, and if he fails, he breaks. As for what neurosis actually is, one must at present take a descriptive point of view, because the cause is unknown. Freud,⁸ who made such a great contribution to the understanding of the psychogenic factors in neurosis, believed that behind the psychologic disorders were humoral and constitutional troubles which would eventually be understood and lead to medical therapy. Other authors accent the constitutional weaknesses of the neurotics,⁹ and some of Freud's followers insist that neurosis is entirely psychogenic. I believe that all one can now say about classification is that neurotic patients are those who suffer from a variety of symptoms which largely group themselves into syndromes well known as "nervousness," "anxiety attacks," "psychosomatic reactions," "reactive depression," "hysteria," "obsessive and compulsive reactions" and "hypochondriasis." The new war experience adds to this list the reactions that have been described here, most of which if seen in civil life one would call "psychotic" until one was surprised by the favorable outcome. In fact, the division of mental disorders into "neurotic" and "psychotic" is arbitrary and fallacious.¹⁰

Some headway has been made in understanding the psychogenic factors in the different neuroses. Freud pointed out various "defense mechanisms" used by neurotic patients and to some extent made his diagnosis on the basis of what sort of "mechanism" the patient employed. Unfortunately he did not make a new nomenclature for the neuroses to fit the psychologic origin, but used old terms in a new way, always a confusing procedure. Nevertheless, some psychologic reactions seem to be somewhat typical of different types of neurosis, for example, the simple expedient of forgetting in the typical hysterical amnesia, the guilt feelings so common in reactive depression and the preoccupation with rituals to ward off anxiety in the compulsive neurotics. Until there is more knowledge about heredity and the psychologic and physiologic

8 Freud, S. *Gesammelte Schriften*, Vienna, Internat Psychoanalyt-Verlag, 1928, vol 11, p 362.

9 Symonds, C. P. Anxiety Neurosis in Combatants, *Lancet* 2 785, 1943. Debenham, G., Hill, D., Sargant, W. W., and Slater, E. *Treatment of War Neurosis*, *ibid* 1 107, 1941.

10 Cobb, S. *Borderline of Psychiatry*, Cambridge, Mass., Harvard University Press, 1943.

6 Sargant, W. Physical Treatments of Acute Psychiatric States in War, *War Med* 4 577 (Dec) 1943.

7 Henderson, J. L., and Moore, M. Psychoneuroses of War, *New England J Med* 230 273, 1944.

mechanism involved in "neurosis," little progress can be made in classification and prevention. Therapy can still go ahead along psychologic lines because psychotherapy has empirically proved itself of value.

EXPERIMENTAL NEUROSIS

There is hope of increased progress in the understanding of the neuroses because of experimental work on animals that seems to throw some light on the physiology and psychology of these conditions. The first step, that of producing in animals a disorder analogous to that seen in man, was accomplished by Pavlov twenty years ago, but did not reach the attention of physicians until Liddell began publishing his pioneering work on "experimental neurosis" in 1927. Liddell and his colleagues have carried on this research up to the present time, and a summarizing paper¹¹ in Hunt's "Personality and the Behavior Disorders" (chapter 12) brings the subject up to date. Not only has Liddell corroborated and expanded Pavlov's observations, but he has shown that some of the concepts were wrong. In the first place, Pavlov was a physiologist who was trying to study one set of functions in the dog in a scientific and impersonal way. He disliked psychology and felt that an exact science must avoid such multiple variables and loose concepts as the psychologists used. Thus he believed that his dogs in the dark and sound-proof room, where they stood in harness on a table and reacted to carefully graded stimuli, day after day, were giving him examples of reflex action cut off from all extraneous stimulation by the environment. It has been one of Liddell's contributions to show that "Pavlov's classical method of the conditioned reflex was not an impersonal observational procedure, but a traumatizing procedure." The very restriction of environment by taking the animal into an enclosure in a small room, the lack of noise, the loneliness, the standardization of procedure and the monotony all affected the animals by limiting their freedom and changing their habits. Not only did their reactions become abnormal while responding to laboratory procedure, but their whole way of life in the barnyard. Liddell has case histories of sheep trained to the laboratory for periods of five to fourteen years. Goats and pigs were also used, the latter being the most resistant to the narrowed environment. But all could be trained with time and patience to stand willingly in the Pavlov frame and wait for the stimuli and re-

warding food. The difficult differentiations given to the animals after they were well trained were no doubt the final precipitants of the "neurotic" reactions, but they were the "last straw" and not the sole cause as Pavlov thought. Liddell says

The situation, as we now view it, appears as follows. Domestication itself imposes upon the animal restrictions and pressures, a hierarchy of them, beginning with the simple physical restraints imposed by the fenced-in area within which the animal lives. It must be recognized that its food is not sought after but is supplied at stated times. It is forced to associate with other animals of its own species and of other species. Crises involving self-defense, reproduction, and food arise from time to time. Then again, the animal assumes a submissive relation to the attendant and experimenter. From this account it can be seen that the perplexing problems which face the animal in the conditioned reflex laboratory represent restraints and pressures situated at the apex of a pyramid. Progressive restriction of liberty and correlative increase in pressures (similar to those exerted by society on the human individual) extend from the wild state, through domestication, to the too refined training of the laboratory.

As training progresses the animal's behavior becomes more predictable and impulsiveness gives place to skill. That is to say, the animal comes to stand quietly in the Pavlov frame and, at the signal intimating the coming shock to the forelimb, it no longer struggles to escape. Instead, it makes a deliberate postural adjustment preparatory to executing a precise series of flexion movements with the member to which the shock is about to be applied.

The daily period of self-imposed restraint to which the animal is subjected in the conditioning laboratory, together with its relinquishment of initiative and spontaneity within the testing period, we now believe, lays the foundation for the pathological outcome of long-continued training. Yet this self-imposed restraint is not of itself sufficient to lead to disturbed behavior.

Sheep and goats subjected to a conditioning regimen that caused them to flex a limb periodically in response to a buzzer noise, after many repetitions would delay the response and prepare the posture of the limb for it, and eventually there would develop a stiffening and motor incapacity of the limb that might last for years. The resemblance to human hysteria is obvious.

Gantt¹² has recently published a monograph on the "origin and development of artificially produced disturbances of behavior in dogs." He brings out many of the points discussed by Liddell, but his dogs were less confined in the experimental situation and the relationship between dog and experimenter was obviously important, even more so than in the experiments of Liddell in which he also appreciated the importance of the "rapport" between animal and experimenter.

Gantt's monograph begins by showing that the method of conditional reflexes is a sound one and brings psychobiology to a high level of scientific

11 Liddell, H. S. Conditioned Reflex Method and Experimental Neurosis, in Hunt,¹³ chap. 12.

12 Gantt, W. H. Experimental Basis for Neurotic Behavior, New York, Paul B. Hoeber, Inc., 1944.

accuracy at which experimental data may be expressed in mathematical formulas. He shows clearly, however, that when one deals with the higher cerebral functions, such as conditioning, generalization concerning responses made as if they applied to all higher mammals or even to one species are fallacious. The problem becomes individual, each animal responds differently at these higher levels, because each animal differs in hereditary makeup and life experience.

Disturbances in behavior that resemble human "neurosis" can be brought about in animals by natural emotional shocks, such as parturition in female dogs, a male dog's being near a female in estrus, fighting and threats to life, as in the famous case in which Pavlov's laboratory was flooded and the dogs nearly drowned. The monograph, however, centers on the acute disturbances artificially produced by the conditioning experiment. The general training situation is recognized by Gantt as abnormal and leading to "neurotic" reactions, but specific experimental procedures are especially discussed, such as the simultaneous excitation of the unconditioned reflexes or the making of a more and more difficult differentiation between two conditioned stimuli. For example, a dog is taught to differentiate between a metronome at the rate of 60 and another at the rate of 144, one means to him "food" and the other "no food." If these signals are given at seven minute intervals he reacts normally and appropriately, but if they are given too close together the dog makes mistakes, does not salivate regularly and then has spells of dyspnea and finally falls asleep on the stand. The dog, "Nick," is the most interesting of the subjects described by Gantt. This animal was trained and precipitated into "neurotic" behavior by causing him to attempt to differentiate between a pair of musical tones.

Nick was a mongrel male born about 1929 or 1930, weight about 12 kg. He was introduced into the laboratory in early 1931 and kept in the paddocks with the other dogs. For about a year before any work was done on him he was brought into the experimental room for casual observation. Nothing was noted then that impressed one as remarkable, in fact, he was selected with Fritz and Peter for laboratory work, as being, according to general appearances, normal. He seemed to be lively and playful, perhaps even more companionable and easy to make friends with than other new dogs.

No careful and detailed examination was made on him prior to experimentation, but it is significant that casually and by the means of ordinary observation he appeared normal, as shown by selection for experiments requiring a normal animal. The contrast between the results of casual observation and the subjection to the rigidly controlled and delicate measurements in the routine of the laboratory deserves emphasis. *It is only by the latter method that we can detect the individual which will show a breakdown under stress.* The early

symptoms seen in the laboratory situation which gave us a clue to the constitutional instability were in Nick (1) refusing to eat, (2) the absence of inhibition of the conditional reflex when the differentiation became hard, the slight conditional reflex at first, and the easy setting in of inhibition, (3) the lack of differentiation, (4) the striking increase of muscular activity and restlessness.

It is remarkable in Nick not only that the nervous symptoms have continued for ten years without repeating the original conflict but that the spread to the urinary and sexual systems did not occur till after 1935, several years after the conflict. That they were related to the conflict is shown by their appearance only in the experimental environment and other relationships to the original stimuli, as will be discussed.

Nick became excited and restless when the environment of the experimental room, or any part of it, was brought to his attention. The experimenters were an important element, and he ignored and gave cold treatment to Gantt even when he had a long rest on the experimenter's farm. Other symptoms were motor tensions, vocalizations, palpitations, dyspnea and anorexia with refusal of food that was in any way reminiscent of the experimental room. Most interesting of all, however, were the sexual reflexes that developed slowly and lasted for years. Erections and even ejaculation would occur when Nick was brought into the experimental room. When he was tested by local application of electrical stimulation to the genitalia it was found that his time of beginning of erection was slightly decreased, the time of duration of erection was greatly reduced and the latent period of ejaculation was shortened. In other words, the disturbing situation in the laboratory gave Nick a syndrome resembling human ejaculatio praecox.

For more details the monograph of Gantt and the papers of Liddell must be consulted. The items here picked out for discussion clearly indicate that a good beginning has been made in the experimental approach to neurosis. Of especial interest (in relation to the discussion under "Neuroses and the War" about the constitutional factor in neurosis) is the agreement of Pavlov, Liddell and Gantt on the importance of the "pre-morbid personality" of the animal, his lability or stability, which according to Gantt can be tested only by special methods and should not be left to general clinical impression as to whether an animal is "nervous" or not.

PERSONALITY

The war, with its need for evaluation of men, has led to a great increase in studies of personality. Leaders must be chosen, men must be picked for aviation, for military government and for a hundred other jobs. This has now brought forth a host of methods and theories, bad and good. The publication of a two volume handbook on "Personality and the Behavior Dis-

orders"¹³ this year has given a sound basis from which students of "personology" may start. The book was put together and edited by Professor Hunt, of Brown University. In volume I there are thirty-five chapters by different authors, taking up theoretic approaches to personality, methods of assessing personality, experimental behavior disorders, hypnotism, heredity and other biologic determinants of personality. In the next volume personality is taken up in relation to infancy and childhood experience, adolescence and culture. The main types of behavior disorder are described by different psychiatrists, and special methods are discussed. The articles are remarkably sound and readable, giving historical summaries and new points of view. There is enough difference of opinion to add spice and show that much is not yet settled. For the physician this is a book with many hours of profitable and enjoyable reading.

NEUROLOGY

The war has also affected adversely the production of neurologic papers. Many of the journals in this specialty are much smaller than they previously were, and some of them have ceased publication altogether. The papers are shorter, and, although many of them are of immediate interest in relation to the war, there is less serious and consecutive work to be reported. Of course, a great deal of research is going on in the armed forces and for the war effort, but this is largely restricted and cannot be published and reviewed at present.

METABOLISM OF THE BRAIN

In looking through the recent neurologic literature, it is obvious that there has been an increase in interest in the subject of cerebral metabolism, especially the use of oxygen by the brain. This has been stimulated in the first place by the work on insulin shock therapy and in the second by the needs of aviation medicine, in which states of anoxia or hypoxia are common. Rossen, Kabat and Anderson¹⁴ have reported new methods for observing the effect of occlusion of the carotid arteries to cause sudden and temporary cerebral anoxia. They made a cuff that fitted around the neck which could be inflated to a pressure of 600 mm of mercury within one eighth of a second. They examined both normal subjects and schizophrenic patients and showed that loss of consciousness in young men appeared

six and eight-tenths seconds after the occlusion of the circulation. This coincided with the appearance of slow waves in the electroencephalogram. Former experimenters had believed that unconsciousness did not occur as rapidly as that and had given such figures as eleven and twenty-one seconds. Gurdjian, Stone and Webster¹⁵ studied the effects of varying degrees of hypoxia on the metabolism of the brain. It is well known that lactic acid and the decomposition of phosphocreatine occur when there is oxygen deprivation in the brain. These authors designed experiments to find the critical oxygen levels at which these changes appear. Dogs were exposed to breathing mixtures low in oxygen for periods of fifteen to sixty minutes. At the level of 11 to 13 per cent of oxygen in inspired air, the lactic acid in the brain increased. This occurred when the oxygen saturation in the arterial blood was between 55 and 65 per cent and that of the venous blood was between 28 and 43 per cent. Decomposition of phosphocreatine began when the oxygen level in the inspired air reached 7 per cent. If the animal was allowed to rebreathe air, resynthesis was complete in about five minutes.

Joseph Wortis¹⁶ studied cerebral oxidation by means of the Barcroft-Waiburg manometer. The material was minced whole brain tissue of adult white rats. He was able to show that the uptake of oxygen had a sharp rise for the first six hours, with a flattening off thereafter. If a small amount of serum was added to the immersion fluid, the oxidation continued at a practically constant rate for the duration of the experiment and did not flatten off at six hours. This might mean that there is in blood serum some essential factor of the oxidative enzyme system.

Chesler and Himwich¹⁷ have studied the glycogen content of the brain and found that each part of the central nervous system possesses a characteristic concentration of glycogen. These values were shown to be relatively constant. In their most recent paper they report trying the effect of insulin hypoglycemia on the glycogen content of parts of the central nervous system of the dog. It was observed that the decrease in glycogen began in the corpora quadrigemina, followed by the cortex, thalamus, cerebrum and medulla, in that order.

¹³ Hunt, J. M. *Personality and the Behavior Disorders*, New York, The Ronald Press Co., 1944.

¹⁴ Rossen, R., Kabat, H., and Anderson, J. P. *Acute Arrest of Cerebral Circulation in Man*. *Arch Neurol & Psychiat* **50** 510 (Nov) 1943.

¹⁵ Gurdjian, E. S., Stone, W. E., and Webster, J. E. *Cerebral Metabolism in Hypoxia*, *Arch Neurol & Psychiat* **51** 472 (May) 1944.

¹⁶ Wortis, J. *Effect of Serum on Survival Time of Brain Tissue and Revival of Cerebral Oxidation*, *Arch Neurol & Psychiat* **51** 176 (Feb) 1944.

¹⁷ Chesler, A., and Himwich, H. E. *Effect of Insulin Hypoglycemia on Glycogen Content of Parts of the Central Nervous System of the Dog*, *Arch Neurol & Psychiat* **52** 114 (Aug) 1944.

These papers are indications of the interest in brain metabolism and of the advances that are being made in that line. To bring this work into relationship with the histopathology of the brain, one has only to turn to the recent experiments of Hurst¹⁸. He gave daily sublethal doses of potassium cyanide to animals and found that after large doses microscopic sections of the brain showed areas of cortical necrosis. With smaller doses given over a longer period, there would be patches of necrosis in the white matter and loss of myelin. With the smallest doses,¹⁹ given over periods of four months or more, there were massive areas of demyelination reminding one of the lesions of Schilder's diffuse sclerosis. These lesions seem to be of the same age everywhere, and because cyanide is known not to accumulate in the tissues, one must conclude that the effect is

18 Hurst, E. W. Experimental Demyelination of the Central Nervous System, *Australian J. Exper. Biol. & M. Sc.* **18** 201, 1940.

19 Hurst, E. W. Experimental Demyelination of the Central Nervous System, *Australian J. Exper. Biol. & M. Sc.* **20** 297, 1942.

due not to an accumulative toxin but to repeated attacks of histotoxic anoxia. Somewhat similar lesions had been caused some years before by Ferraro²⁰. Hurst's work elaborated on the earlier experiments and succeeded in producing lesions with a number of histotoxins. Besides the potassium cyanide, he used sodium azide, hydroxylamine, ethylcarbanate (urethane) and pentobarbital sodium. It was his belief that these drugs inhibited one or another of the various enzyme systems and that the lesions came from the resulting lack of oxygen.

The common demyelinating diseases, especially the noninfectious encephalitides, multiple sclerosis and Schilder's disease, are all of unknown cause. These advances in the understanding of cerebral metabolism and of the effect of inhibiting oxygen uptake may eventually lead to a better understanding of the origin of these obscure conditions.

20 Ferraro, A. Experimental Toxic Encephalomyelopathy, *Psychiatric Quart.* **7** 267, 1933, *Experimental Toxic Encephalomyelopathy*, *Arch. Neurol. & Psychiat.* **29** 1364 (June) 1933.

News and Comment

PENICILLIN AND WARFARE

Supplement to the July 1944 Issue of the *British Journal of Surgery*

A supplement to the July 1944 issue of the *British Journal of Surgery* presents a symposium on Penicillin in Warfare, including reports of clinical experiences of a preliminary nature in the treatment of recent war wounds in the field with penicillin. It contains a foreword by Major General L. T. Poole on the successful employment of penicillin in the most forward surgical units as a prophylactic against wound sepsis. General Poole says that in some instances a long interval must elapse before definitive surgical procedures can be undertaken and that penicillin can be used to bridge this gap and delay, modify or even prevent the development of sepsis.

Florey and Jennings point out that the substance is the most powerful antibacterial agent which has been brought into clinical use and that it will completely inhibit the growth of the most sensitive organisms, such as gonococci and staphylococci, when diluted at least 1:500,000,000.

Lieutenant Colonel Jeffrey discusses the specific action of penicillin against the common bacterial invaders of war wounds (staphylococci and clostridia in the early stages and streptococci in the later stages) and expresses the opinion that it is the most effective and least harmful agent yet discovered. The drug has three main spheres in war surgery: (1) to prevent early infection of a wound, (2) to control infection in the first two weeks—this is the sphere in which the greatest value can be expected from penicillin—and (3) to combat sepsis in the later stages.

Lieutenant Colonel Bentley reports on a series of 200 consecutive casualties with flesh wounds treated by early secondary suture with local application of penicillin and states that primary healing was obtained in 190 (95 per cent).

Lieutenant Colonel Brown reports much the same results. He feels that the results are so good and the period of morbidity so lessened that all soft tissue wounds, however small, should be sutured with the aid of penicillin. He warns, however, that penicillin has in no way replaced and can never be a substitute for thorough primary surgical treatment.

Furlong and Clark state that penicillin failed to control sepsis fully and did not diminish the incidence of chronic infection in open fractures of the femur. They therefore stress that penicillin is not a substitute for surgical intervention and that the greatest care and attention must be given to surgical technique and to fundamental surgical principles.

Jeffrey believes that penicillin has a definite place alongside surgery and antiserum in the treatment of gas gangrene.

D'Abreu and his associates have been particularly impressed with the capacity of the pleural cavity to retain instilled sodium penicillin for as long as three days. They recommend that in the forward areas the attempt to prevent infection of hemothoraxes should consist in thorough aspiration combined with instillations of penicillin, which they feel would offer the best hope of preventing the present high rate of hemothorax infections seen in the theater of war.

Major Robinson, of the United States Army, reports on 1,000 patients with sulfonamide-resistant gonorrhea treated with penicillin, 94.7 per cent of whom were free of gonorrhea after one course of treatment of 100,000 units given intramuscularly in 10,000 unit doses every hour or in 20,000 unit doses every three hours. The remaining patients required a second course of penicillin, varying from 100,000 to 150,000 units.

Wise and Pillsbury, of the United States Army, confirm in general the report of Mahoney and his associates on the rapid spirocheticidal effect of penicillin in human beings, the prompt regression of early lesions and the absence of significant reaction to treatment.

Book Reviews

Infectious Anemias Due to Bartonella and Related Red Cell Parasites David Weinman In Transactions of the American Philosophical Society, 1944' New Series, Volume 33, Part III Price, \$1 25 Pp 108 Philadelphia American Philosophical Society, 1944

Human bartonellosis, although confined today to areas within Peru, Colombia and Ecuador, is a disease of great clinical and epidemiologic interest. It is unique in that hitherto it has not spread from these Andean regions, a feature which doubtless depends on its low infectivity and the importance of the insect vector, a species of phlebotomus fly, in transmission to man. Weinman's monograph offers in detailed and authoritative fashion what is known of this interesting malady. The two manifestations of human bartonellosis, namely, a severe febrile anemia and a benign eruption, are separately presented in their varied forms and complications. Much is still obscure in the epidemiology of the disease. There is no doubt that all naturally contracted infections are conveyed by the sandfly, direct contagion is rare, although Carrion, at the cost of his life, proved that direct inoculation of infectious material is successful and, as early as 1885, showed that the infectious agents of verruga peruana and Oroya fever are the same.

Hemobartonella and animal bartonellosis are presented in the second chapter. Infectious anemias of animals caused by micro-organisms parasitizing the erythrocytes seem to be fairly common, they comprise three genera: Grahamella, Eperythrozoon and Hemobartonella. With the possible exception of Eperythrozoon, none of them affects man, however, they are interesting in that they belong, with Bartonella, in that relatively small class of infectious agents that grow in or on red cells.

Weinman describes, in the third chapter, the species of Eperythrozoon and the diseases they cause in animals. These pathogens affect mice and other rodents, and sheep and cattle. Splenectomy precipitates violent infections. Organic arsenicals rapidly sterilize infections with Eperythrozoon and Hemobartonella, but they have no effect on infections caused by Grahamella and little or none on bartonellosis of man.

The public health aspects of human bartonellosis are discussed in the last chapter. Severe epidemics with a high mortality rate have been observed, in one instance 4 per cent of the population died from the disease in one year. The disease is especially violent among newcomers to endemic areas and in new populations in nonendemic zones. Prior infections seem to confer some degree of resistance to an individual, however, persons who have recovered may act as carriers for months or perhaps years. Public health measures must prevent contact between sandflies and man. Since these insects are night biters, these measures may include (a) leaving the endemic region at nightfall, (b) use of bed nets and (c) construction of fly-proof buildings. The best measure of all is the removal of the entire population from the infected areas. Economic considerations and the habits of the people will make these measures hard to apply.

This publication is recommended to all who are interested in the infectious anemias of man and animals. It contains much information originally recorded in foreign journals, more important, however, is that this

and much other information have been carefully assembled and presented in an orderly and systematic fashion.

Clinical Tropical Medicine By twenty-seven authors and edited by Z. Taylor Bercovitz, M.D. Price, \$14 Pp xvii + 957, with 121 illustrations and 20 plates New York Paul B. Hoeber, Inc., 1944

This volume, written with good editorial cohesion by a group of experts, covers the field of tropical medicine in an altogether satisfactory manner. It is comprised of eleven sections, which seem to divide the broad subject of the book in a logical way. Thus diseases characterized by diarrhea or caused by protozoa, spirochetes or rickettsias or of any other known cause are grouped together. And since the book is designed for the clinician, all the diseases described are considered in the uniform style that a clinician likes, first with a historical note and then with succeeding paragraphs on etiology, epidemiology, pathology, symptomatology, diagnosis, prognosis, treatment and prevention. At the end of each chapter is a short bibliography.

All the authors are well known and are thoroughly familiar with the subjects allotted to them. The editor has managed to make the text read as if it were written by a single person. The illustrations, on the whole, are clear and help materially in elucidating the appearance of lesions or parasites which will be no more than names to many readers.

Dr. Wilbur Sawyer, of the International Health Division of the Rockefeller Foundation, has written a foreword. He points out that most American physicians and medical students have until now felt no urge to familiarize themselves with exotic and tropical diseases. War, however, has suddenly brought a departure from this medical isolationism. There is now a pressing demand for authoritative and practical instruction in the treatment and prevention of diseases of the warm countries.

This book, therefore, well put together as it is, is certain to be useful to a wide variety of readers. It is less bulky and more easy to manage than the larger works on tropical medicine, at the same time it is a good deal broader and more comprehensive than are the epitomes which have appeared recently. It deserves a high degree of popularity.

The Urinary Tract. A Handbook of Roentgen Diagnosis By H. Dabney Kerr and Carl L. Gillies Price, \$5.50 Pp 320, with numerous illustrations Chicago The Year Book Publishers, Inc., 1944

The Year Book Publishers have embarked on the manufacture of a series of short handbooks dealing with roentgenologic diagnosis. This volume, which is listed as sixth in the series, considers the urinary tract.

It is a workmanlike affair copiously illustrated with excellent reproductions of films. There are four major divisions of the subject matter: the kidney, the ureter, the bladder and the urethra. The text describes these anatomic units from a radiologist's point of view, describing first what is considered their normal visualization and then various deviations from the normal.

On pages opposite to the text are reproduced characteristic roentgenograms, which illustrate with delightful clarity the points in the text that appear to deserve greatest emphasis

The book is so clearly written that it is easily read, and the illustrations are particularly good. On the whole, this small handbook is bound to be a popular adjunct to any hospital library. It will be useful to students and interns and to such inquisitive staff members as still attempt to see for themselves how the master radiologist interprets his findings in facing the baffling diagnostic problems afforded by diseases of the genitourinary tract.

Clinical Syphilology By John H. Stokes, Herman Beerman and Norman R. Ingraham, Jr. Price, \$10. Pp 1332, with 911 illustrations. Philadelphia: W. B. Saunders Company, 1944.

Stokes's "Clinical Syphilology" has really become an institution in American medicine in the sense that there is no other work which fully takes the place of this outstanding treatise. Dr. Stokes's lucid and vivid style relieves the text of the monotony so to be dreaded in large monographs. Every phase of the subject is thoroughly gone into—bacteriology, clinical features, theory and practice of treatment and public health aspects. The numerous illustrations, tables and summaries enrich and enliven the text.

The fact that Stokes has worked in such harmony with other outstanding American syphilologists makes what he has to say even more impressive, since the work represents, as the writer says in his preface, to some extent a synthesis of experience. It is somewhat appalling to find that 1,300 pages must be devoted to the discussion of one disease, even though it is a very important one. As Dr. Stokes optimistically points out, it is to be hoped that penicillin or some similar agent will so alter the situation as materially to simplify the whole subject.

Heart Disease By Paul Dudley White, M.D. Third edition. Price, \$9.00. Pp 1025. New York: The Macmillan Company, 1944.

The third edition of this standard work on diseases of the heart needs no introduction to the medical profession. It has been for nearly fifteen years probably the most popular book on cardiac disorders that the medical profession makes use of in teaching and in practice. It is almost encyclopedic in content, it is complete in every respect. Only one or two criticisms may be pertinent. In the first place, the list of references after each chapter is extensive. To the student, at least, a few well selected references might be of greater value than a list of some thirty to one hundred articles. Many of these articles are good, but some are better than others, and only the best should be listed for the uncritical reader or the tyro.

Another minor criticism is the weight of the book, almost 3 pounds (1.3 Kg), which makes for a great deal of difficulty in reading unless there is some kind of support other than the unaided arms. These criticisms are of minor importance and do not negate the essential value of this well written, authoritative, extremely detailed and comprehensive book on cardiac disease.

Proteins and Amino Acids. Physiology, Pathology, Therapeutics Pp 189, with 5 illustrations. Yonkers, N. Y.: The Arlington Chemical Company, 1944.

Although sponsored by the Arlington Chemical Company, this little book contains no advertising matter. It consists of a good practical summary of current knowledge about proteins and their breakdown products and metabolism. It should be a useful compendium for persons who wish to orient themselves as to the newer aspects of protein therapy in connection with surgical operations, burns and fractures.

TWO CASES OF MORVAN'S SYNDROME OF UNCERTAIN CAUSE

HARRY PARKS, M.D., AND O. S. STAPLES, M.D.

ATLANTA, GA

BOSTON

About ninety years ago, Augustin Morvan, a Breton physician, was consulted by a fisherman with a septic finger. Morvan incised it and noted that his surgical manipulations caused no pain. The patient did not even wince at the contact of the bistoury. This phenomenon appeared so curious that Morvan determined to investigate the sensibility of the affected hand, to his surprise he discovered that the hand and a part of the forearm did not feel the prick of a pin. During the next thirty years he observed 6 other similar cases of painless infections of the hand, and these he reported in 1893 in the *Gazette hebdomadaire de médecine et de chirurgie*¹ as examples of a new disease. He called this condition *parésie analgésique des extrémités supérieures*.

Morvan's paper is interesting. He expressed the opinion that the source of this new disease must lie in the spinal cord, and he emphasized the dissociated sensation which his patients exhibited. "The patient can hold a burning coal in his hand without pain. Yet the feeling of touch is preserved, and the patient, his eyes blindfolded, can indicate with precision the spot where he is touched." He described the paresis and amyotrophy which were apparent in many of his patients and their various trophic disorders, such as deformed extremities, peculiar arthropathies and spontaneous fractures.

This paper stimulated great interest at once. Since its publication there has grown up a large literature on "Morvan's disease." As a rule the clinical picture of which Morvan wrote has been proved to be due to syringomyelia, with trophic lesions an outstanding feature. That leprosy may produce nearly identical symptoms has been mentioned many times, in fact, several writers have suggested that the sailors of Brittany are peculiarly liable to an atypical form of leprosy exemplified in the cases which Morvan described,

and thus the leprosy of Brittany has been discussed seriously in the French literature.

A few authors have insisted that the clinical picture of Morvan's disease is not always due to syringomyelia or to leprosy and that in some cases it represents an independent disorder. Two cases of this type have been studied carefully by us in Boston, one at the Robert Dawson Evans Memorial and the other at the Children's Hospital. In both the diagnosis of syringomyelia seems improbable, the fundamental disease apparently being an unusual neuropathy of undetermined origin. These cases are reported to stimulate interest in a rare and little understood condition.

REPORT OF CASES

CASE 1—G. A., an 8 year old American boy, entered the Robert Dawson Evans Memorial on July 22, 1936.

His father and mother and one sister were living and well.

History—The boy's delivery and his early history were normal. He had measles when he was 4 years old, chickenpox at 5 years of age and probably one-sided mumps at 7. Except for these illnesses his history was uneventful. There was no delay in walking and no mental retardation. There was no history of injury to his spine. He attended grade school and appeared to be bright and intelligent in his school work.

When the boy was 2 years old his mother noticed that he often bit and chewed his finger tips until they bled. The resultant wounds appeared to be painless and healed slowly. In those early days, also, he burned his hands several times without seeming to be aware of it. When he was 6 years old an infection developed about the nail of the right index finger. This was not painful and apparently was not accompanied by any systemic reaction. Roentgenograms of the finger showed osteomyelitis of the terminal phalanx, and this was removed. Several months before his admission to the hospital sensation in his legs seemed to become abnormal. He stumbled and fell more often than did other children of his age, and often he injured his toes, though never in such a manner as to make him complain of pain. Six months before he entered the hospital his left index finger became infected, and presently the terminal phalanx dropped off. Just before the patient came under our observation several shallow ulcerations developed on his finger tips. These healed slowly with callus-like thickening of the skin. His hands became so awkward in finer movements such as writing, buttoning his clothes and cutting food that his parents determined to send him to a hospital for treatment.

¹ Morvan, A. De la parésie analgésique à panaris des extrémités supérieures ou parésie analgésique des extrémités supérieures, *Gaz hebdomadaire de médecine et de chirurgie* 20: 580-583, 590-594 and 624-626, 1893.

Physical Examination—He appeared a fairly well developed but undernourished youngster, bright and intelligent. His posture was poor, with bowing of the legs and protrusion of the abdomen, but there was no obvious scoliosis. His heart, lungs and abdomen were normal. The axillary and inguinal glands were easily palpable and were firm, small, discrete and nontender. The peripheral arteries were not unusual.

The hands and feet showed a curious variety of trophic changes, which were more marked in the upper extremities than in the lower. The nails were short, thick and dark, and several were cracked and loosely attached to their matrices. The skin surrounding the nails was thickened as if it were mildly and chronically inflamed. The finger tips were rough and keratotic. There were no folds of skin over the terminal interphalangeal joints. On both thumbs and over three fingers of the right hand near their tips were small, shallow ulcers surrounded by thickened skin and extending through the subcutaneous tissues. There were many healed scars on the lower parts of both legs. The toes looked much as did the fingers but did not appear so badly damaged.

Neurologic Examination—Examination of the nervous system revealed glove-like areas of hypesthesia or anesthesia involving both hands below the wrists and both feet and legs below the knees, with diminished reactions to pain, touch and temperature stimuli in these regions. Such hypesthesia was more marked distally than centrally, and the disturbances in the sensation of touch were more widely distributed than were the disturbances in the sensation of pain and temperature.

There was total absence of all superficial and deep tendon reflexes. No abnormal reflexes were elicited except Romberg's sign. Vibratory sensation and stereognosis seemed impaired, and it seemed probable too that the sense of muscle and joint positions was impaired. No muscular atrophy or fibrillary twitchings were observed.

The muscles and ligaments about both ankle joints were lax, permitting undue inversion and eversion of the ankle joints.

The vasomotor reactions in the hands and feet were not remarkable as judged by measurements of the temperature of the skin, which were made at the Peter Bent Brigham Hospital. There was no tremor.

Examination of the cranial nerves gave negative results except that the corneal reflexes on both sides were diminished, with slightly diminished sensitivity to pain and temperature in the face.

Laboratory Studies—A variety of laboratory studies gave negative results. Blood counts, urinalysis, examinations of stools and chemical examinations of the blood, including determinations of phosphorus and calcium, gave normal results. Repeated Wassermann, Hinton and Kahn tests of the blood serum revealed no abnormalities. Lumbar puncture revealed a clear and colorless spinal fluid which was under normal pressure and had normal dynamics. It contained 3 cells per cubic centimeter and had a total protein concentration of 9 mg per hundred cubic centimeters. The colloidal gold curve and the Wassermann reaction of the spinal fluid were normal.

Roentgenograms of the hands and feet showed lack of tufting of the ends of the distal phalanges but were otherwise not remarkable. Roentgenograms of the cervical, thoracic, lumbar and sacral vertebrae revealed no pathologic changes. There was no scoliosis or spina bifida.

Biopsies of skin taken from the dorsa of the wrists and from the middle finger of the right hand were not

informative. No lepra cells or lepra bacilli were seen, and there were no histologic changes to suggest the presence of syphilis or of tuberculosis.

Examination of the amputated left thumb and middle finger showed thickening of the skin due to cornification of the surface epithelium and edema of the corium. No nerves or nerve filaments were seen. Microscopically there was found to be chronic inflammation of the skin.

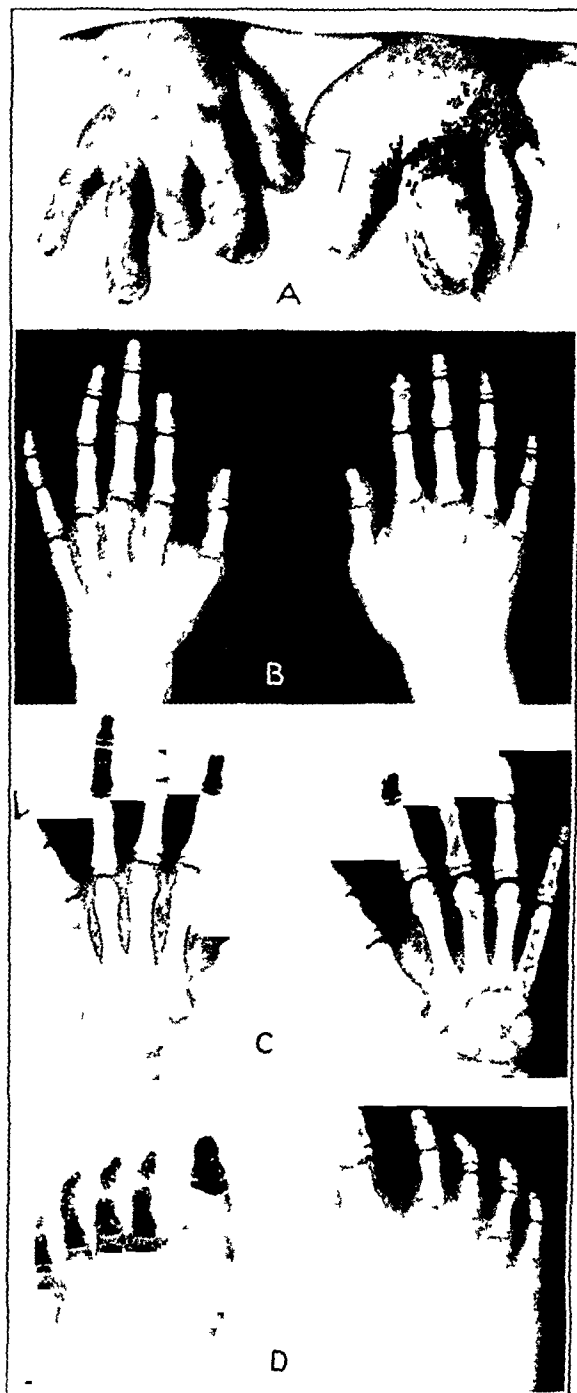


Fig 1 (case 1)—A, hands, showing painful infections and their end results and abnormal nails. There is no muscular atrophy. B, C, roentgenograms of the hands, showing progressive changes in bones in the course of two years. D, roentgenograms of the feet, showing undeveloped phalangeal and metatarsal bones with pressure necrosis of the proximal phalanges.

and of the subcutaneous tissues with infiltration of neutrophils, eosinophils and endothelial cells. There was disappearance and degeneration of the medullated nerves, which were surrounded by a dense fibrous capsule and by lymphocytes, plasma cells and endothelial cells. The

phalanges showed marked atrophy and decalcification without periosteal reaction or osteomyelitis. An occasional arteriole was almost completely occluded by fibrosis and lymphocytic infiltration.

In 1943 biopsy of the small nerve of the right foot was performed at another hospital. This was reported to show no inflammatory changes.

Course—Up to the time of writing the patient's subsequent history has consisted of repeated painless infections of the fingers and hands following minor trauma. At one time he bit off a small portion of the tip of his right middle finger. An infection followed, with much edema and necrosis of the soft tissues, until finally the terminal phalanx of this finger was found lying loose in the tissues and was removed. This episode was followed by a palmar abscess, which was drained without anesthesia. It was only on very deep probing that there was any complaint of pain. On another occasion an infection of the left thumb and of the right middle finger developed. The thumb required amputation at the metacarpophalangeal joint and the finger at the proximo-interphalangeal joint. Cultures from these wounds contained hemolytic streptococci and *Staphylococcus aureus*. Six months after the first examination his condition was about as it had been except that only greatly diminished biceps reflexes were obtainable for a time. The spinal fluid was reexamined and was entirely normal.

On the hypothesis that the child might have syringomyelia and that radiation might be of some therapeutic help, he was given a course of roentgen treatment of the spinal cord. The benefit obtained from this was by no means striking or certain.

A report seven years after the patient was first seen revealed that his general health was good. Recurrent ulcerations of the finger tips and further loss of three additional phalanges had occurred, also he has had trouble with both feet.

CASE 2—J. P., a 12 year old American girl, entered the Children's Hospital on July 27, 1938. It may be of some interest that her parents were first cousins. She had three brothers and one sister, who were living and well. One sister had died in infancy of some undetermined cause.

History—The patient had had measles, mumps, whooping cough and scarlet fever in infancy. Her social background was notably poor, so that her diet had often been inadequate for varying lengths of time.

Three and a half years before entering the hospital she began to have weakness in her legs and recurrent painless ulcerations and infections in her fingers and toes.

Physical Examination—She was fairly well developed and well nourished and appeared normally intelligent. Her posture was good, and there was no demonstrable scoliosis. Examination of the heart, lungs and abdomen revealed no abnormalities.

The skin about the nails of both hands was thickened, reddened and cracked, and the nails were short and irregular. Her feet showed symmetric equinovarus deformities, which could not be corrected by passive motion. There were large calluses over the lateral plantar aspects of both feet, with numerous fissures in the skin of this region. On the right foot there was an ulcer, which appeared to be chronically infected.

Neurologic Examination—Neurologic examination revealed symmetric glove-like areas of anesthesia or of diminished sensitivity to pain, temperature and touch, involving all four extremities and most marked distally. The disturbances in the sensation of touch were more

widely distributed than the disturbances in the sensations of pain and temperature. Bone conduction seemed normal, although sense of position was lacking in the fingers and toes. The deep tendon reflexes were diminished, and no abnormal reflexes were obtained. The cranial nerves seemed normal.

There was symmetric weakness of the anterior tibio-peroneal muscles, of the extensors of the toes, of the short and long toe flexor muscles of both feet and of the palmar interosseous muscles of both hands. There was no obvious muscular atrophy, however, and no twitching or tremor. There was no evident vasomotor abnormality.

Laboratory Studies—Just as in the other case, all laboratory studies gave negative results. The spinal

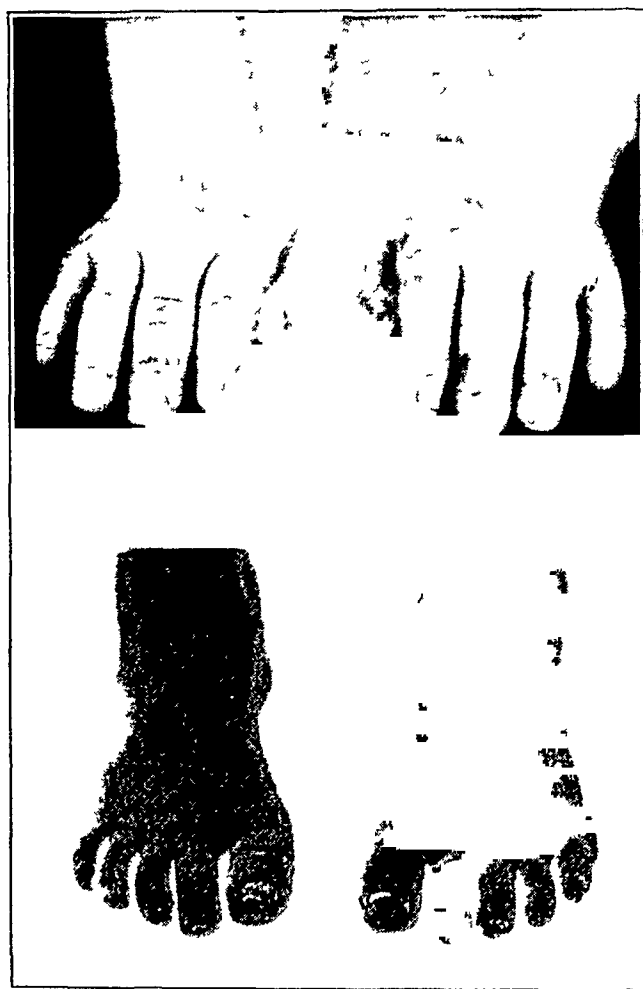


Fig 2 (case 2)—Hands and feet, showing abnormal nails. There is no muscular atrophy.

fluid was normal. Roentgenograms of the spine, the chest, the arms and the legs were normal except for the absence of "tufting" of the ends of the terminal phalanx of the right great toe and of the left middle finger. There was no scoliosis or spina bifida.

Specimens of skin taken from the left forearm and from the right foot in the region of the ulcer revealed nothing remarkable on histologic examination. Stains for tubercle and lepra bacilli revealed no organisms, and tuberculosis did not develop when material from these tissues was inoculated into a guinea pig. Biopsy of a section of the saphenous nerve just above the ankle gave negative results.

Course—A report from this patient three years later indicated that there had been no appreciable change in her condition. Striking changes in the bones of the feet, apparently of a trophic nature, had developed.

These 2 cases, clearly, have several common features. In each there was a symmetric peripheral type of hypesthesia involving all four extremities, more marked distally than centrally, and accompanied by peculiar trophic changes

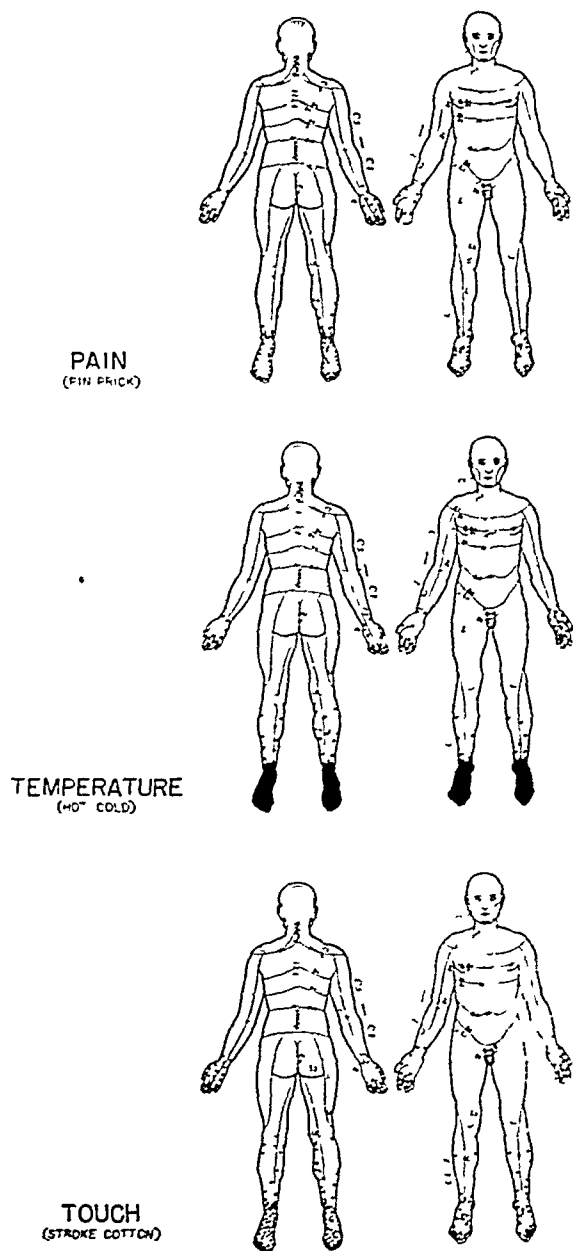


Fig 3 (case 2)—Chart showing the distribution of anesthesia and hypesthesia. Black indicates areas of anesthesia, dots areas of hypesthesia. The findings in case 1 were essentially identical.

Neurologic examination gave negative results in other respects except that all deep reflexes were either diminished or absent. Roentgenograms revealed as an early lesion loss of tufting of the terminal phalanges in the hands and feet. There was a varying degree of muscular weakness without apparent muscular atrophy. Biopsies of the skin were not informative, and in 1 case examination of a peripheral nerve gave no remarkable results. Attempts to prove the presence of tuberculosis or of leprosy yielded negative results.

SIMILAR CASES IN THE LITERATURE

We have reviewed all the reports of "Morvan's disease" occurring in children. We believe that 7 cases resembling ours have been described and that they do not present the clinical picture ordinarily associated with syringomyelia. A summary of these cases follows.

Head² has described the case of a 4 year old girl whom he saw because of frequent falls and painless injuries of the hands and feet. When she was 8 months old she had an infection of the right index finger, which was slow in healing, later she had successive infections of all her fingers, at one time losing a thumb spontaneously as a result of a simple paronychia. When Head saw her all of the terminal phalanges were lost, there was no sensation of pain or of temperature in the arms or the legs, and the deep tendon reflexes were absent. There was no muscular atrophy, but the patient's gait was unsteady. The cranial nerves seemed normal.

Bousquet³ reported a case of a 9 year old girl who when she was 3 years old had a painless burn on the finger, resulting in an infection which healed slowly. When she was 4 years old she began to bite her finger nails to the point of bleeding, without experiencing any pain. When she was 6 years old she had a painless wound of the left heel, which required frequent incisions for drainage. There were trophic changes in both hands, since all the nails had disappeared. Sensory examination revealed absence of the sensations of pain and temperature below both knees and both elbows, although tactile sensation was intact. In this case the reflexes of the tendons and the skin were normal.

Bonnett and Goyet,⁴ Bonnett^{4a} and Delore, and Barbier and Jarricot^{4b} reported a case which was followed for twenty-three years. When first observed the patient had sensory and trophic disturbances of the hands and feet. There was symmetric loss of the sensations of pain and temperature in the hands, with preservation of tactile sense, but all forms of sensation were lost in the feet. The deep reflexes were absent.

2 Head, H. Morvan's Disease. Case Report, *London Hosp Gaz* **10** 5-7, 1903.

3 Bousquet. Un cas de syringomyelie chez l'enfant, *Ann de med et chir inf* **10** 673-679, 1906.

4 Bonnett, L. M., and Goyet. Syringomyelie a forme de maladie de Morvan chez un enfant, *Lyon med* **113**. 1017-1020, 1909.

4a Bonnett, L. M. Syringomyelie a forme de maladie de Morvan traite par la radiotherapie bon resultat, *Lyon med* **130** 1051-1054, 1921.

4b Barbier, M., and Jarricot, H. Sur un de "syringomyelie a forme de Morvan," *Lyon med* **148** 374-377, 1931.

in the legs, although they were present in the arms. He was given several courses of roentgen therapy without any noticeable effect. Several years later, when he was 20 years old, he improved for a period of three years although roentgenograms of the phalanges showed characteristic resorption of bone. Later there was exacerbation of the process with recurrence of trophic changes in the feet. When he was 36 years old the disturbances in sensation were

Cruchet, Petges and Joulia⁵ have studied a 7 year old boy who at the age of 3 began to have "indolent blisters" on his arms and legs, these were followed by painless ulcers and subsequent loss of several phalanges. The fingers and toes were short and thick. The movements of the hands were awkward. On the palmar surfaces of the feet were perforated ulcers, which at times had drained bony fragments, so that some of the toes were reduced to conical stumps.

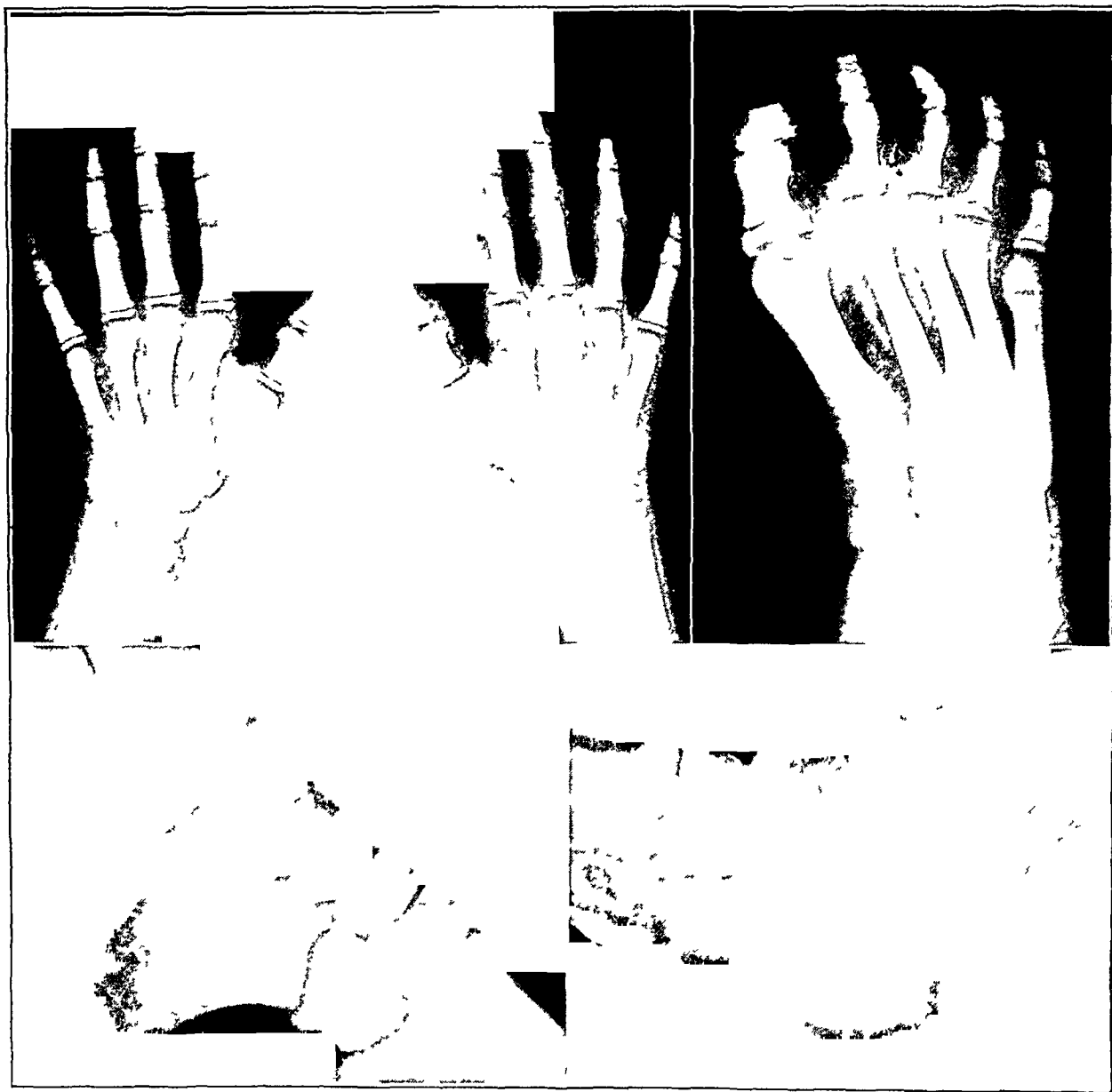


Fig 4 (case 2)—Roentgenograms of the hands and a foot. The early lesion appears to be loss of tufting of the terminal phalanx, shown in the left middle finger and great toe. The roentgenograms of the foot show progressive changes in bone in eighteen months. There have developed condensation and destruction of the talus and to a lesser extent of the os calcis and of the navicular. There is moderate osseous debris in the region of condensation. The worse involved foot appeared normal when the patient was first seen.

unchanged. Both knee jerks were absent, although the left ankle jerk was obtainable. There was no muscular atrophy, and his general health was good. This case has been followed over a longer period than any other case recorded. The striking feature of it is the small apparent progress of the disease during more than twenty years.

The deep reflexes were absent. There was loss of all forms of sensation below the knees and wrists, with diminution of sensation from the knees to the hips and thighs and from the wrists

⁵ Cruchet, R., Petges, G., and Joulia. Un cas de maladie de Morvan chez un enfant de sept ans, *Bull et mem Soc de méd et chir de Bordeaux*, 1920, pp 282-290.

to the forearm. Lepra bacilli were not found in the discharge from the ulceration or in the nasal discharge. The Wassermann reactions of the blood and the spinal fluid were negative.

Wagner⁶ reported the case of a 15 year old girl who began to have painless blisters and ulcers of the toes when she was 9 years old. The terminal phalanges of the large toes were absent, and ulcerations were present on their palmar surfaces near the bases. There was no muscular atrophy. The hands had a diminished sensation of temperature, although the senses of pain and touch were normal, and in the feet the sensations of both temperature and pain were less acute than the normal though not entirely absent. Roentgenograms of the feet showed destruction of the phalanges and of the metatarsal bones.

Gaté and Riou⁷ reported 2 cases, the patients being a brother and a sister. The man who was 27 years old when he was first examined, gave a history of having been unable to feel heat for many years and as a result having experienced many painless burns. When he was 13 years old he had a nonpainful swelling in the right knee and a year later a similar process in the left knee. At 17 he had a series of painless perforated ulcers of the feet, so that finally, when he was examined, both index fingers, the middle finger of the right hand, the first and second toes and the terminal phalanx of the third toe of the right foot were absent. There was a perforated ulcer of the right heel. The sensations of pain and temperature were absent below the knees and elbows and diminished proximally. The sensation of touch was but little impaired. The reflexes were normal. There was no muscular atrophy or scoliosis. The spinal fluid was normal, and the Wassermann reaction of both the blood and the spinal fluid was negative.

This man's sister was first seen when she was 38 years old. Her difficulties began when she was about 13 and appear to have been much like her brother's. Eventually all her fingers became affected, she lost one foot and had only two toes on the other. In this patient there were no abnormal reflex changes and there was no muscular atrophy.

COMMENT

Each of these 7 cases reported by foreign authors appears to us much like the 2 studied in Boston. Whatever the disease may be, it

⁶ Wagner, I. Beitrag zur familiären lumbosacralen Syringomyelie, *Monatschr f Kinderh* 53: 137-152, 1932.

⁷ Gate, J., and Riou, J. Troubles trophiques et troubles de la sensibilité réalisant un syndrome de Morvan familial, *Lyon med* 157: 102-106, 1936.

appears to develop in young people of either sex. The first symptoms are sensory and usually consist of absence of pain with burns or other injuries. Later there develops loss of the sensation of pain, temperature and usually touch in the distal parts of all four extremities. Trophic changes soon become prominent in the form of ulcers, atrophy of the bones and changes in the nails, spontaneous amputation of small parts becomes necessary by reason of infection. On physical examination the superficial and deep



Fig 5—The late result of Morvan's syndrome in a patient known to have had the disease for fourteen years. The patient was seen by Dr. Cruchet, who has permitted us to use the illustration.

tendon reflexes may be absent, diminished or normal. No paralysis, muscular weakness or atrophy develops, and evidence of involvement of the upper motor neurons or of the lateral or the pyramidal tract is strikingly absent. The course of the disease appears to be relatively

benign. Unfortunately observations at necropsy have not been described.

Questionnaires were sent to several authors who reported the cases described, asking for follow-up notes and particularly for results of necropsy. These letters elicited no significant information. The 1 case which was followed for more than twenty years, however, and the history of our own cases suggest that any rapid progressiveness is unlikely.

The authors whose cases have been mentioned discussed them as problems in differential diagnosis, hypertrophic neuritis, leprosy, Raynaud's disease and syringomyelia. The preferred diagnosis in each instance was syringomyelia.

Compared with cases of syringomyelia as usually reported, these cases seem somewhat atypical. In syringomyelia there frequently is a segmental distribution of dissociated sensation, that is, preservation of the sense of touch with loss of the sense of pain and temperature in a given area. In this group of cases there was impairment of all forms of sensation, occurring symmetrically in all four extremities. In syringomyelia there are likely to develop signs of involvement of the lateral column, such as exaggerated reflexes or spasticity, signs of involvement of the anterior horn, such as loss of reflexes, atrophy or fibrillations, and signs of involvement of the posterior horn, such as loss of the sense of position and loss of vibratory sensations. These changes appear either singly or in combination in the majority of cases of syringomyelia. Such manifestations, on the whole, were strikingly absent in our cases. The distribution of the neurologic signs of syringomyelia is usually asymmetric. In these cases the symmetry of the involvement was striking. Syringomyelia follows a course which is chronic and slowly progressive but often more rapid than that in the cases reported here seems to have been. While trophic changes such as those in our cases have been observed frequently in typical cases of syringomyelia, such trophic phenomena are an additional element in the picture of syringomyelia and do not dominate the clinical picture as much as in the cases described here.

In our 2 cases biopsies were of little assistance. The exact diagnosis remains obscure. If our patients have some form of peripheral neuritis,

it is an unusual form unless one assumes that the sensory rather than the motor fibers are predominantly affected. On the other hand, if they have a form of syringomyelia, it is also an unusual form of this disease and unlike that in most of the cases reported.

A few years ago Dr. René Cruchet, then professor of medicine at the University of Bordeaux spoke in Boston on Morvan's disease and allowed us to study his manuscript. He saw our patient, G. A., and suggested an interesting possibility. He did not think this boy had syringomyelia though he agreed that he had a form of Morvan's disease, or, as he preferred to call it, Morvan's syndrome. He wondered whether the young man's condition could have arisen from a lesion located in the so-called trophic center of the medulla, an area which was mapped out by Laruelle⁸ to include the nucleus of the lateral cornua and the superior sympathetic nucleus of Jacobson. Cruchet expressed the opinion that this area exists. He hypothesized that an inflammatory or degenerative lesion or even a congenital imperfection sharply localized to this area might result in extraordinary trophic disturbances, by postulating a lesion in that region he explained in a more or less plausible manner the development of the picture of Morvan's syndrome in persons without apparent syringomyelia or leprosy.

How seriously such an apparently fanciful suggestion should be taken is uncertain. Seemingly, however, there is a peculiar neurotrophic disorder of unknown cause occurring in children which runs a chronic course. It is characterized by symmetric loss of sensation in the arms and legs and by notable trophic changes. It may resemble certain forms of syringomyelia but lacks the characteristic segmental distribution of sensory symptoms with dissociated sensation which is ordinarily found in this disease. It lacks also amyotrophy, spasticity and other signs indicating involvement of the upper or lower motor neurons or of the spinal tract. It is not leprosy. It is a rare disease, which warrants further study.

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8 Laruelle, L. La structure de la moelle epiniere en coupes longitudinales, *Rev. neurol.* 67: 695-725, 1937.

PNEUMOCOCCIC ENDOCARDITIS

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SAN FRANCISCO

Graves¹ in 1843 offered what was probably the first description of this disease. He reported the observations at autopsy in a case of pneumonia and described endocarditis of a bicuspid pulmonary valve.

The great increases in information concerning bacterial endocarditis which were made in the latter half of the nineteenth century were ushered in by Ormerod's Goulstonian Lecture of 1851.¹ Here, for the first time, a clear distinction was drawn between ulcerative and rheumatic endocarditis. The basis of the clinical recognition of bacterial endocarditis was established firmly by Kirkes in 1852.² He described embolic phenomena in various forms, occlusion of the arteries of the leg, hemiplegias and cutaneous petechiae and argued that these were due to mechanical obstruction of the vessels by pieces detached from the "large fibrinous masses on the heart valves." Stokes³ in 1854 defined endocarditis and stated that "there is no pathognomonic sign of its existence, and its diagnosis depends on the recent production of a valvular murmur or the existence of special morbid states of the system, which predispose to inflammation of the heart." Wilks in 1868³ reemphasized Kirkes' studies and also pointed out that valvular endocarditis may act as "a wound at the center of the circulation" and so by dissemination of purulent infarcts give the symptoms of "pyemia."

The ensuing years mark the great growth of the science of bacteriology, and in 1875 Klebs first described the pneumococcus. In 1881 Pasteur and Sternberg, working independently, isolated pneumococci for the first time through animal passage. In April 1884 Fraenkel⁴ made the first report of his studies, which were to fulfill later (1886) all of Koch's postulates. He

demonstrated the diplococci in lesions of endocarditis, pleuritis, pericarditis and nephritis and correctly assumed that metastases might arise from a pulmonary lesion.

During this time clinical studies had been keeping abreast of increasing bacteriologic knowledge. Osler in 1881⁵ spoke of finding "micrococcus balls" in 4 cases of endocarditis complicating pneumonia. He was not ready to assert that the "micrococcus balls" were the cause of the disease, but called attention to the frequency with which this condition and meningitis accompany pneumonia. One year later Bozzolo⁶ concluded from clinical observations that pleurisy, pericarditis, endocarditis and meningitis were frequently associated with lobar pneumonia and that this association was due to a single infective agent. Netter⁷ in 1886 published a comprehensive review of ulcerative endocarditis as a complication of pneumonia. He demonstrated pneumococci in the vegetations and in the blood stream and produced the disease experimentally.

INCIDENCE

Pneumococcic endocarditis is generally considered a relatively rare disease, almost a medical curiosity, although medical literature contains numerous reports of individual cases. In 1885 Osler⁶ reported 16 instances identified in 103 necropsies on patients who had died of lobar pneumonia. In one of the classic papers on the subject of infectious endocarditis Thayer⁷ described 38 cases of pneumococcic endocarditis of his own and an additional 41 cases collected from the literature. These represented respectively 12.4 per cent and 14.7 per cent of 306 personal cases and 538 collected cases of all kinds of bacterial endocarditis. Perry¹ in his monograph "Bacterial Endocarditis" collected 1,000 cases in which the causative bacterial agents were

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1 Perry, C. B. *Bacterial Endocarditis*, Bristol, John Wright & Sons, Ltd., 1936, p. 137.

2 Willius, F. A., and Keys, T. E. *Cardiac Classics*, St. Louis, C. V. Mosby Company, 1941, p. 473.

3 Willius and Keys,² p. 577.

4 White, B. *The Biology of Pneumococcus*, New York, The Commonwealth Fund, 1938, p. 799.

5 Gordon, A. *Acute Endocarditis*, *Canad. M. A. J.* **42**: 182 (Feb.) 1940.

6 Osler, W. *Malignant Endocarditis*, *Lancet* **1**: 416, 459 and 505, 1885.

7 Thayer, W. S. *Bacterial or Infective Endocarditis*, *Edinburgh M. J.* **38**: 237 (April), 307 (May) 1931.

well established In 112 (11.2 per cent) the disease was due to the pneumococcus Goldburgh, Baer and Lieber^{7a} found that in 62 of 646 cases (9.6 per cent) of acute bacterial endocarditis observed in 26,007 autopsies done over a twenty year period the pneumococcus was the infecting organism Table 1 shows the incidence of pneumococcic endocarditis among pneumococcic infections in general^{7b} and among pneumococcic infections in patients on whom autopsies were performed^{7c}

MATERIALS FOR THE PRESENT STUDY

The present is a statistical and clinical study of 16 patients with pneumococcic endocarditis Autopsies were performed on 13 of these patients, constituting 0.25 per cent of 5,503 consecutive autopsies (1933-1944) There were 118 cases of

Data from the cases of 3 additional patients will also be used Permission for autopsies on 2 of these patients could not be obtained The third patient is living and is receiving penicillin therapy

PATHOLOGY

The vegetations in pneumococcic endocarditis vary greatly in size, color and distribution Thayer⁷ stated that "the process is, almost invariably, an acute ulcerative endocarditis especially notable for early and extensive destruction of tissue resulting in erosions of valves with aneurysms, rupture or burrowing ulcers" Ruegsegger⁸ agreed closely with this conclusion The vegetations vary in size from a mere excrescence to a huge growth that fills a ventricle almost completely The masses are usually soft, friable

TABLE 1—Incidence of Pneumococcic Endocarditis Among Pneumococcic Infections in General and Among Pneumococcic Infections of Patients Subjected to Autopsy

Author	Number of Cases of Pneumococcic Infections	Number of Cases of Pneumococcic Endocarditis	Percentage of Pneumococcic Endocarditis	Number of Cases of Pneumococcic Infections Identified at Autopsy	Number of Cases of Pneumococcic Endocarditis	Percentage of Cases of Pneumococcic Endocarditis Identified at Autopsy
Rosenbluth (1932)	150	5	3.3			
Ruegsegger (1938)	655	19	2.9			
Moore (1940)	1,469	54	3.6			
Osler (1885)				103	16	15.5
				(lobar pneumonia)		
Lord (1932)				337	14	4.15
				(lobar pneumonia)		
Finland (1937)				684	31	4.5
Goldburgh (1942)				1,041	62	5.9
				(lobar pneumonia)		
Tinsley (1944)				118	13	11.0
				(lobar pneumonia)		

lobar pneumonia (2.1 per cent of all cases in which necropsies were performed) There were 36 cases (0.65 per cent of all the cases in which necropsies were performed) of acute bacterial endocarditis for which the cause was considered definitely established by clinical examinations and necropsy In these, 13 infections were due to the staphylococcus, 2 to the gonococcus, 8 to hemolytic streptococci and 13 to the pneumococcus (36 per cent)

7a Goldburgh, H., Baer, S., and Lieber, M. Acute Bacterial Endocarditis of the Tricuspid Valve, *Am J M Sc* **204** 319 (Sept.) 1942

7b Moore, F. J., Thomas, R. E., Kistler, M., Ireland, R. M., and Hallstone, V. E. Pneumococcic Pneumonia, *Arch Int Med* **66** 1290 (Dec.) 1940
Rosenbluth, M. B. Pneumococcus Endocarditis, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 3, p. 983

7c Finland, M., Brown, J. W., and Ruegsegger, J. M. Anatomic and Bacteriologic Findings in Infections with Specific Types of Pneumococci, Including Types I to XXXII, *Arch Path* **23** 801 (June) 1937

and grayish red The pneumococcus may attack the endocardium, leaving the valves intact

Table 2 shows the site of the pneumococcic valvulitis as given in series of autopsies presented by various authors The well known predilection of the pneumococcus for the valves of the left side of the heart is illustrated However, Goldburgh, Baer and Lieber⁵ and Allen⁹ felt that this organism produces a relatively greater number of right-sided lesions than do other organisms causing acute bacterial endocarditis The former authors found vegetations restricted to the tricuspid valve in only 1.9 per cent of 584 cases of acute bacterial endocarditis due to infec-

8 Ruegsegger, J. M. Pneumococcic Endocarditis, *Arch Int Med* **62** 387 (Sept.) 1938

9 Allen, A. A Case of Bacterial Endocarditis Illustrating the Mechanism of Localization and Nature of the Vegetations, *Am Heart J* **21** 667 (May) 1941, Mechanism of Localization of the Vegetations of Bacterial Endocarditis, *Arch Path* **27** 399 (March) 1939, Nature of the Vegetations of Bacterial Endocarditis, *ibid* **27** 661 (April) 1939

tive agents other than the pneumococcus, while in 14 per cent of the cases of pneumococcic endocarditis there were vegetations of this type

In 77 per cent of the patients in the present series pneumococcic masses were confined to the aortic and the mitral valve, these patients constituted 54 and 23 per cent respectively of the total number. Involvement of the tricuspid valve alone was seen in only 1 patient, 7 per cent of the total number. The remaining 2 patients showed lesions of both the aortic and the tricuspid valve. In 6 of the 7 patients in whom there was involvement of only the aortic valve perforation of a cusp occurred. This also took place in 1 of the 3 patients who had vegetations only on the mitral valve. An aortic cusp was eroded in each of the patients in whom there were lesions of both the aortic and the tricuspid valves.

2 patients on whom autopsies were not done or in the third patient, now receiving treatment. Thus it is seen that the incidence of previous valvular damage given by Thayer (37.5 per cent) and that demonstrated by the present series (46 per cent) agree moderately well and are in sharp contrast to the incidence reported by Ruegsegger (66 per cent).

The data available are all based on series that are fairly small and are therefore influenced greatly by individual cases. It is apparent also that the majority of the cases of pneumococcic endocarditis occur on valves undamaged previously. Perhaps, however, the high proportion of instances in which the valves were damaged should be more strongly emphasized and the clinician should be especially concerned with the possibility of the development of pneumococ-

TABLE 2—Site of Acute Pneumococcic Endocarditis

Site of Cardiac Lesion	Thayer		Goldburgh		Ruegsegger		Lord		Tinsley		Combined	
	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
Left side	30	81	46	74	13	86	18	78	10	77	117	78
Right side	3	8	9	15	1	7	1	13	1	7	17	11
Both sides	4	11	7	11	1	7	2	9	2	16	16	11
Total no. of cases	37		62		15		21		13		150	

Acute Valvulitis	Goldburgh		Ruegsegger		Tinsley		Combined	
	Cases	%	Cases	%	Cases	%	Cases	%
Aortic	18	29	7	46	7	54	32	36
Mitral	23	37	4	27	3	23	30	33
Tricuspid	9	14	1	7	1	7	11	12
Aortic and mitral	5	8	2	13			7	8
Aortic and tricuspid	3	5	1	7	2	16	6	7
Mitral, aortic, tricuspid	1	2					1	1
Mitral, tricuspid, pulmonie	1	2					1	1
Mitral, aortic, tricuspid, pulmonie	2	3					2	2
Total number of cases	62		15		13		90	

Preexisting valvular disease is believed to have little effect on whether acute valvulitis is to occur. Thayer⁷ found that in 37.5 per cent of 38 cases there was evidence of previous valvular damage. Ruegsegger⁸ found that antecedent valvular disease existed in but 1 of 15 cases, reported by him, of pneumococcic endocarditis in which autopsies were performed. Davis and Weiss¹⁰ reported that in only 7 of 5,215 cases in which autopsies were performed was there acute endocarditis secondary to a pneumonic process, the entire complex occurring, apparently, on previously normal valves. However, in the present series 6 of 13 patients on whom autopsies were performed showed either clinical or histologic evidence of preexisting valvular disease. There was no evidence of antecedent valvular disease in the

cic endocarditis in a patient who has had valvular disease or who has a convincing history of a disease that produces damaged valves.

It is beyond the scope of this paper to give an extended discussion of the experimental production of the method of localization of bacterial endocarditis. However, the condition can be produced experimentally on previously undamaged valves by repeated injections of bacteria. Wright,¹¹ using streptococci and pneumococci, found that infection of the valves of the hearts of rabbits is most likely to occur in animals so treated with vaccines that demonstrable antibodies are present in the blood stream at the time of injection. Wadsworth¹² has described similar

10 Davis, D, and Weiss, S. The Relation of Subacute and Acute Bacterial Endocarditis to Rheumatic Endocarditis, *New England J Med* 208:619 (March 23) 1933.

11 Wright, H. D. Production of Experimental Endocarditis with Pneumococci and Streptococci in Immunized Animals, *J Path & Bact* 29:5 (Jan) 1926.

12 Wadsworth, A. B. A Study of the Endocardial Lesions Developing During Pneumococcus Infections in Horses, *J M Research* 39:279 (Jan) 1919.

findings—the development of bacterial endocarditis in horses being immunized against the pneumococcus. Keefer¹³ stated that it seems significant that the valves became infected only after the antibody titer became high, the antibodies aiding in the clumping and localization of the bacteria. He further stated that the equine endocarditis demonstrated by Wadsworth “corresponds closely to cases of endocarditis in man in which lesions develop on previously normal heart valves, for most of the patients have had bacteremia and have developed antibodies.”

As for the selective localization on the valves of the left side of the heart, Rueggesser⁸ suggested that this is no more than should be expected, since in most cases the lungs are the portal of entry. A theory which has long been held is that the higher pressure in the left lung in some way contributes to lower resistance in the tissue. A possible explanation for the increased incidence of valvular lesions of the right side of the heart in pneumococcic endocarditis is that offered by Allen.⁹ He expressed the view that all vegetations are produced and localized as the result of “impact, pressure, and contact” of the blood stream and the valves of the heart and that previous damage to valves serves to augment these forces. However, as the virulence of the infecting organism increases, “the necessity for pressure, impact, and contact diminishes,” and it is less necessary that there be a previously damaged valve for the bacteria to lodge on. It is to this increased virulence of the infecting organism that he attributed the increased incidence of valvular involvement of the right side by such organisms as the pneumococcus.

CLINICAL FEATURES

The range of ages in the 16 patients was from 27 to 84 years, the average being 50 years. Eleven of the patients were above 45 years of age. The observation that acute pneumococcic endocarditis is a disease primarily of the fourth, fifth, sixth and seventh decades has been a remarkably constant feature of all studies on this subject. This is in contrast to the well known fact that subacute bacterial endocarditis is primarily a disease of younger persons. Twelve of the patients were men, and 4 were women. That they were all white is presumably due to the low proportion of other races in our service.

Lord¹⁴ stated that in about one third of the cases of pneumococcic endocarditis the portal of

entry is not definite. Thayer⁷ found that in 83.3 per cent of his 38 cases the disease followed pneumonia. In 79 per cent of the cases reported by Rueggesser⁸ acute bacterial valvulitis followed lobar pneumonia. In the present study it was found that in 12 patients (75 per cent) pneumococcic endocarditis followed lobar pneumonia and that in 2 there was associated pneumococcic meningitis. In 1 patient the condition started with acute otitis media and mastoiditis. In the remaining 3 patients (19 per cent), including 1 having pneumococcic meningitis, no obvious portal of entry could be found.

Clinical evidence of cardiac disease was suggested by modest cardiac enlargement in 4 patients. One patient, 84 years of age, was known to have myocardial disease, for electrocardiograms taken ten years previously had shown a defect in intraventricular conduction. Repeat tracings during his final illness showed no changes. Two patients were reported to have a loud, musical systolic murmur, heard over the entire precordium. In only 1 patient is irregularity of rhythm reported to have developed during the course of the disease. In this instance auricular fibrillation was diagnosed clinically, digitalis was given and the rhythm reverted to a sinus mechanism within twenty-four hours. In this patient there was associated acute purulent pericarditis and myocarditis.

At necropsy, however, the weights of 7 hearts were found to be 400, 420, 460, 500, 520, 520 and 660 Gm respectively. No explanation could be found for the hypertrophy in 1 patient, a 28 year old man. The enlargement in 5 cases was considered to be due either to mild valvular disease or to arteriosclerotic heart disease. In the remaining patient, a 27 year old man, autopsy revealed endocarditis of the mitral valve with fenestration of a cusp, great hypertrophy and dilatation of the left auricle, and embolism of the left descending coronary artery with myocardial infarction.

Purpura was present during the course of the illness in only 5 patients. The spleen was palpable in but 2 patients. Yet at autopsy the spleen was considerably enlarged, those of 5 patients weighing from 330 to 430 Gm each. Clubbing of the fingers was noted only once, and this was in the patient with the longest clinical course, probably seventy to seventy-five days.

A remarkably constant feature was the presence of the development of hypochromic anemia. It was not unusual for the patient's hemoglobin to decrease by 25 per cent and reach a level that demanded repeated transfusions. The number of

13 Keefer, C. S. Pathogenesis of Bacterial Endocarditis, *Am Heart J* **19** 352 (March) 1940.

14 Lord, F. T. Pneumococcus Endocarditis, *New England J Med* **207** 767 (Nov 3) 1932.

leukocytes was below 10,000 in but 2 instances, 1 of which was a terminal manifestation of the overwhelming infection. One patient repeatedly showed over 40,000 leukocytes, the highest total being 46,800. The vast majority of the counts were between 20,000 and 25,000. There was invariably an increase in the number of polymorphonuclear leukocytes and nearly always an increase in the number of banded forms.

Three of the 16 patients showed numbers of red cells in the urinary sediment. Red blood cell casts were not demonstrated. In 2 patients acute embolic focal nephritis was demonstrated at autopsy. In 1 of these cases the blood urea was 41 mg per hundred cubic centimeters of blood, and in the other it was 91 mg per hundred cubic centimeters at the patient's entry into the hospital and rose terminally to 126 mg. The microscopic hematuria present in the third patient may have been the result of the therapy with sulfonamide compounds. In a fourth instance the blood urea was 135 mg per hundred cubic centimeters, but subacute glomerulonephritis was found that seemed surely to antedate the terminal illness.

In all but 1 case cultures of the blood showed the growth of pneumococci. In the majority of instances other studies on the sputum, the empyema fluid, the cerebrospinal fluid and the pericardial fluid were also done. In every case the same organism was identified from all mediums. The following types of pneumococci were found by culture of the blood: group IV, five times, type XII, three times, type XXV, two times, and types I, VII, X, XVIII and XX each once. In 1 case the organism was cultured from the valves of the heart at necropsy, morphologically and culturally it was a pneumococcus which did not show capsular swelling with the serums of types I, II or III.

The signs of acute pneumococcic endocarditis usually appear shortly after the onset of the pneumococcic infection. However, they may follow by days or even weeks what has appeared to be an uncomplicated recovery from such an infection. If the valvulitis merges with the acute pulmonary, meningeal or mastoid infection, the diagnosis is very likely to be overlooked. The onset is usually abrupt and ushered in with a sudden rise in temperature and possibly a chill. It may follow an afebrile period. It may happen during defervescence from pneumonia. From this point on the temperature is nearly always continuously elevated. Paroxysms of shaking chills and fever are not uncommon. There are usually a marked aggravation of the patient's symptoms and the signs of profound toxemia.

The course is usually a rapidly fatal one. Thayer⁷ found that 88 per cent of patients live less than four weeks and 92.5 per cent less than two months. The patients in the present series were hospitalized on account of their fatal illness over periods as short as two days and as long as fifty-one days. As nearly as could be determined, the length of their present illness varied from seven to approximately seventy days. It is not implied that acute endocarditis was in existence for the longest periods, for it is impossible to be sure of the exact point at which valvulitis began. Most deaths from this disease are due either to great toxemia or to meningitis. Thayer⁷ found that 55 per cent of his patients had terminal meningitis, and he expressed the opinion that this is one of the distinctive features of this disease. Ruegsegger⁸ found that 68 per cent of the patients in his series died of meningitis. In the present study 5 of 15 patients died with meningitis. Two deaths were in part due to cardiac insufficiency, and in both patients aortic insufficiency had developed as a result of the ulceration of one or more valve cusps by the infectious process.

DIAGNOSIS

The signs and symptoms necessary for the diagnosis of acute pneumococcic endocarditis are in most respects no different from those needed to establish the diagnosis of subacute bacterial endocarditis. However, it must be remembered that such signs as splenomegaly, purpura and infarction of various organs do occur in a probably significantly smaller number of cases of pneumococcic endocarditis than of subacute bacterial endocarditis. Furthermore, evidence of preexisting valvular disease is present in only a fairly small percentage of the cases of pneumococcic valvulitis. One of the most necessary features for the confirmation of the diagnosis is to obtain growth of the pneumococcus in a blood culture. Prolonged pneumococcemia is in itself presumptive evidence of the presence of this disease.

One sign that is extremely helpful and that will definitely establish the diagnosis is the development of a cardiac murmur indicative of organic valvular disease. Ruegsegger⁸ found that in 7 of his 19 patients aortic incompetency developed during their illness. The long, blowing murmur of aortic insufficiency developed in 11 of 16 patients of the present series. The time at which this murmur was first heard varied from the second to the fifty-first day in the hospital. Aortic insufficiency developed in 6 of the 7 patients that were shown at necropsy to have vege-

tations isolated to that valve. It was heard in all but 1 patient in whom autopsy disclosed perforation of an aortic cusp (8 of 9 patients). In both of the patients on whom autopsy could not be performed because permission was denied and in the patient now under treatment aortic diastolic murmurs developed and persisted. Once established, the murmur did not wax or wane in intensity appreciably. A developing or changing systolic murmur of mitral insufficiency did not help in the diagnosis of the condition of any patient in this series, in spite of the fact that autopsy disclosed 1 patient to have ulceration and fenestration of a mitral cusp. In no instance did the low-pitched, rumbling, crescendo murmur characteristic of mitral stenosis develop as in the case reported by Scott,¹⁵ in which the vegetations on the mitral valves actually produced an effective stenosis.

The development of the murmur of aortic incompetency is so common that it must be regarded as a diagnostic feature of this disease. In every case of pneumococcic infection in which recovery is not rapid and complete the physician should make a painstaking search for this murmur with a diaphragm stethoscope over the entire precordium. Repeated readings of the blood pressure may give the first indication that aortic insufficiency has developed, by showing lowered diastolic pressure and increased pulse pressure. This should serve to make cardiac auscultation even more thorough.

THERAPY

Prevention, not cure, must be the goal in the therapy of pneumococcic endocarditis—prevention by means of early recognition and adequate treatment of pneumococcic infections. For the results of any treatment are disappointing once valvulitis has developed. Indeed, the physician has little to offer but continued endeavor. The sulfonamide drugs have seemingly made no difference in the uniformly fatal outcome of these cases, and added serum therapy has not been demonstrated to be efficacious. Penicillin perhaps will offer a new and potent form of therapy. The general measures for the care of the patient are in no way distinctive and need no discussion here.

15 Scott, T. Pneumococcic Endocarditis. A Report of Two Cases with Some Unusual Features, *Internat. Clin.* **2** 223 (June) 1941.

16 Wells, E. F. Endocarditis as a Complication of Pneumonia, *J. A. M. A.* **39** 978 (Oct. 18) 1902.

Apparent cures have occurred. Wells,¹⁶ Preble¹⁷ and Laubry and Coffin¹⁸ have all reported cases which seem clinically to have been instances of this disease and in which recovery took place. In these cases acute endocarditis with development of aortic insufficiency and embolic phenomena followed what was diagnosed as lobar pneumonia. In all cases the cardiac murmur persisted. Blumberg, Heine and Lipshutz¹⁸ have recently reported a case in which there were multiple embolic manifestations, meningitis, a loud, harsh systolic apical murmur and growth of pneumococci, type XXVIII, in blood cultures on the thirty-sixth day of the patient's hospitalization. The positive blood cultures were obtained after the meningitis had cleared and after protracted treatment with both sulfadiazine and sulfathiazole and after many previous blood cultures had failed to reveal either aerobic or anaerobic organisms. Five hundred and forty thousand units of type-specific serum was given in the first seven days after the blood culture became positive, and administration of sulfathiazole was continued. More recently Keefer¹⁹ has reported a cure with penicillin. In this instance acute endocarditis followed lobar pneumonia, and the murmur of aortic insufficiency developed during the course of the therapy. The murmur persisted after the patient's recovery. Loewe, Rosenblatt, Greene and Russell²⁰ have added the sixth apparent cure, that of a child with congenital heart disease whose blood culture showed growth of pneumococci, type XXVII, and who had pulmonary infarcts. Combined penicillin and heparin therapy was used.

SUMMARY

Pneumococcic endocarditis occurs in about 3 to 3.5 per cent of all pneumococcic infections and is responsible for probably about 5 to 10 per cent of deaths due to pneumococcic infections. The aortic and mitral valves are infected in 36 and

17 Preble, H. B. Pneumococcus Endocarditis, *Am. J. M. Sc.* **128** 782 (Aug.) 1904.

18 Laubry and Coffin, cited by Blumberg, N., Heine, W. I., and Lipshutz, J. Pneumococcus (Type XXVIII) Endocarditis with Recovery, *J. A. M. A.* **120** 607 (Oct. 24) 1942.

19 Keefer, C. S., Blake, F. G., Marshall, E. K., Lockwood, J. S., and Wood, W. B. Penicillin in the Treatment of Infections, *J. A. M. A.* **122** 1217 (Aug. 28) 1943.

20 Loewe, L., Rosenblatt, P., Greene, H. J., and Russell, M. Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis, *J. A. M. A.* **124** 144 (Jan. 15) 1944.

33 per cent of the cases respectively. In only approximately 11 per cent of the cases are the valves of the right side of the heart solely involved. Antecedent valvular damage is present in a minority of the instances but is present often enough—perhaps in one third of the cases—that it may well contribute to the development of this disease. Purpura, splenomegaly and infarction of organs by emboli are less common than in subacute bacterial endocarditis. The ulcerative infectious process often produces fenestra-

tion of a valve cusp, with subsequent appearance of the murmur of aortic insufficiency. A thorough search for this murmur should be made in every case of pneumococcal infection which does not give evidence of rapid and complete recovery. Pneumococcemia is almost invariably present, and repeatedly positive blood cultures are presumptive evidence of the existence of this disease. The disease is usually rapidly fatal and may terminate in acute purulent meningitis. Treatment has so far been highly unsatisfactory.

BRONCHIECTASIS FOLLOWING ATYPICAL PNEUMONIA

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During the past year 45 patients have been treated for bronchiectasis. The symptoms in 20 of these patients followed attacks of atypical pneumonia occurring during the winter of 1942-1943. It is with these 20 patients whose bronchiectasis appears to have been related to atypical pneumonia that this paper is primarily concerned. In 3 of the 20 patients, the bronchiectasis appeared to be reversible as confirmed by subsequent bronchograms. These 3 patients showed less severe cylindric bronchiectasis, confined mainly to the larger bronchi. The remaining 17 patients had more extensive bronchial and bronchiolar destruction, and the damage appeared to be permanent. The diagnosis of atypical pneumonia was made at the time of the original illness, prior to transfer to this hospital, and was concurred with only after careful reexamination of the clinical records and roentgenograms. It is impossible, with the material available to us to determine the general incidence of bronchiectasis following atypical pneumonia, for only the patients for whom this diagnosis was already established or suggested or who had persistent evidence of unresolved pneumonia were transferred.

Prior to pneumonia these patients had no symptoms relative to the pulmonary system. The roentgenograms made at the time of the patients' induction were obtained, reexamined and found to be entirely within normal limits. The attacks of atypical pneumonia were typical for this condition in every respect except that they failed to show spontaneous healing in the usual period. After the acute episode subsided, a cough remained which became increasingly productive. Basilar rales persisted in the affected lungs. Serial roentgenograms showed an unresolved pneumonia. These signs and symptoms continued for a number of months, and the presence of bronchiectasis was confirmed by bronchography.

Eight additional patients with bronchiectasis also claimed attacks of pneumonia in the Army to be the precursor of their cough and sputum. However, 6 of these patients gave histories of pneumonia during childhood, and reexamination of 5 of the 8 induction roentgenograms revealed

suggestive evidence of pathologic pulmonary conditions existing at that time. One must be careful in stating that the attack of so-called atypical pneumonia was the precursor of the bronchiectasis and not in itself atypical because of preexisting bronchiectasis.

The remaining 17 patients with bronchiectasis either had vague histories as to the onset and duration of symptoms or fell into the more common group of persons whose symptoms had been present for years. The majority of these patients had had several attacks of pneumonia. The induction roentgenograms suggested the presence of bronchiectasis in many instances.

Bronchiectasis is a chronic disease characterized by persistent cough, foul sputum and general debility. The symptoms are usually present for a number of years before medical relief is sought. Perry and King¹ stated that 42 per cent of their 167 patients with bronchiectasis dated the onset of the disease to the first decade of life. Similar percentages have been recorded by other observers. Farrell² listed 54 per cent, Ogilvie³ 66 per cent, Ballou, Singer and Graham⁴ 54 per cent and Riggins⁵ 41 per cent of their patients as having had the onset at this time. The majority of the remaining patients dated the onset of their symptoms of bronchiectasis from three to ten years prior to being seen by these authors and frequently considered their condition to be a result of previous attacks of pneumonia or infections of the respiratory tract. It is rare for patients with bronchiectasis to be seen whose cough, sputum and general debility have been of only several months' duration.

1 Perry, K. M. A., and King, D. S. Bronchiectasis. A Study of Prognosis Based on a Follow-Up of 400 Patients, *Am Rev Tuberc* **41** 531-548 (May) 1940.

2 Farrell, J. T. The Importance of Early Diagnosis in Bronchiectasis, *J A M A* **106** 92-96 (Jan 11) 1936.

3 Ogilvie, A. G. Natural History of Bronchiectasis. Clinical, Roentgenologic and Pathologic Study, *Arch Int Med* **68** 395-465 (Sept) 1941.

4 Ballou, H., Singer, J. J., and Graham, E. A. Bronchiectasis, *J Thoracic Surg* **1** 154-193 (Dec) 1931.

5 Riggins, H. M. Bronchiectasis. Morbidity and Mortality of Medically Treated Patients, *Am J Surg* **54** 50-66 (Oct) 1941.

The shortness of the interval between the pneumonia and the onset of symptoms suggestive of bronchiectasis in this group, the fact that as far as could be ascertained there were no symptoms to suggest bronchiectasis prior to the pneumonia and the additional factor of normal roentgenograms taken at the time of induction into the Army stimulated my interest as to whether bronchiectasis could actually result from atypical pneumonia. With the easily available facilities of Army hospitals, bronchograms were made soon after the onset of symptoms suggestive of bronchiectasis. This may account for the short duration of symptoms between the attack of pneumonia and the diagnosis of bronchiectasis in these patients. If bronchographic examinations had been done earlier in other series of patients, the duration of symptoms prior to such a diagnosis would undoubtedly have been materially shortened.

It must be stated at the beginning that there is only one sure means of ascertaining the presence or absence of bronchiectasis, and that is bronchography. Since none of these patients had had bronchographic examinations prior to the onset of atypical pneumonia, it cannot be stated with certainty that they did not have preexisting bronchiectasis. One can only say that there was no reason to suspect this condition of having preexisted.

The purpose of this paper is the presentation of evidence to show that atypical pneumonia may present the factors frequently considered in the pathogenesis of bronchiectasis, namely, bronchial infection and obstruction. Case histories of patients having bronchiectasis following atypical pneumonia will be presented, with their serial bronchograms and pathologic observations. It is difficult to evaluate the role of the secondary bacterial invaders following in the path of the atypical pneumonia in the genesis of bronchiectasis, but it is felt that the atypical pneumonia is at least the initiating factor.

ATYPICAL PNEUMONIA

A knowledge of the fundamental aspects of atypical pneumonia is essential to an understanding of the processes involved in the development of bronchiectasis. Bowen⁶ was among the first to recognize atypical pneumonia as a new disease entity. He described this condition as being an "acute influenzal pneumonitis," a benign type of bronchopneumonia occurring in soldiers stationed in Hawaii. Allen⁷ in 1936 character-

ized the disease as an "acute interstitial pneumonitis." Others⁸ have considered it to be a viral pneumonia. No attempt will be made to discuss the causation. Suffice it to say that the majority of observers believe that the condition, in the present state of knowledge, is best named "primary atypical pneumonia, etiology undetermined." The disease has epidemic potentialities and may cause illness of varying severity up to and including death. Whether this is a new disease entity or not is probably still open to question. A review of the literature shows that there are a number of etiologic agents capable of producing this clinical picture. Similarly, influenzal bronchopneumonia as seen in World War I has been described as an atypical pneumonia by a number of observers.⁹ Certainly, atypical pneumonia as described today in its more severe and protracted forms is similar in many respects to influenzal bronchopneumonia, except that the latter condition in the epidemic form appeared to be more virulent and associated with a higher mortality. It will be remembered that pathologically bronchiectatic bronchi were not an uncommon condition following that disease.

Atypical pneumonia is usually described¹⁰ as a mild to a moderately severe illness affecting

8 (a) Adams, J. M., Greene, R. G., Evans, C. A., and Beach, N. Primary Virus Pneumonitis. Comparative Study of Two Epidemics, *J. Pediatr.* **20**: 405-420 (April) 1942. (b) Reimann, H. A. An Acute Infection of the Respiratory Tract with Atypical Pneumonia. Disease Entity Probably Caused by a Filtrable Virus, *J. A. M. A.* **111**: 2377-2384 (Dec. 24) 1938. (c) Reimann, H. A., Havens, W. P., and Price, A. H. Etiology of Atypical ("Virus") Pneumonias, *Arch. Int. Med.* **70**: 513-522 (Oct.) 1942. (d) Reimann, H. A. Viral Pneumonias, *Bull. New York Acad. Med.* **19**: 177-181 (March) 1943.

9 Norris, G. W., and Landis, H. R. M. Diseases of the Chest and the Principles of Physical Diagnosis, ed. 4, Philadelphia, W. B. Saunders Company, 1931.

10 (a) McCarthy, P. V. Primary Atypical Pneumonia of Unknown Etiology, *Radiology* **40**: 344-346 (April) 1943. (b) Haight, W. L., and Trolinger, J. H. Primary Atypical Pneumonia, Etiology Unknown, *U. S. Nav. M. Bull.* **41**: 988-1000 (July) 1942. (c) Dingle, J. H., Abernethy, T. J., Badger, G. F., Buddingh, G. J., Teller, A. E., Langmuir, A. D., Rueggesser, J. M., and Wood, B. W. Primary Atypical Pneumonia, Etiology Unknown, *War Med.* **3**: 223-248 (March) 1943. (d) Zimmerman, J. J. Viral Pneumonia, *Am. J. Nursing* **43**: 141-144 (Feb.) 1943. (e) Smiley, D. F.; Showacre, E. C.; Lee, W. F., and Ferris, H. W. Acute Interstitial Pneumonitis. A New Disease Entity, *J. A. M. A.* **112**: 1901-1904 (May 13) 1939. (f) Murray, M. E., Jr. Atypical Bronchopneumonia of Unknown Etiology Possibly Due to Filterable Virus, *New England J. Med.* **222**: 565-573 (April 4) 1940. (g) Suttentfield, F. D. Primary Atypical Pneumonia (Virus Pneumonia), *Mil. Surgeon* **93**: 360-364 (Oct.) 1943. (h) Grieco, E. H., Cove, A. M., and Klein, E. C. Pneumonia. A Survey of One Hundred and Six Cases, *ibid.* **93**: 364-367 (Oct.) 1943.

6 Bowen, A. Acute Influenza Pneumonitis, *Am. J. Roentgenol.* **34**: 168-174 (Aug.) 1935.

7 Allen, W. H. Acute Pneumonitis, *Ann. Int. Med.* **10**: 441-446 (Oct.) 1936.

young adults, persisting from five to fourteen days and uninfluenced by chemotherapy. The onset is insidious in some patients, while in others the illness begins with an acute nasopharyngitis, a dry cough that is occasionally productive, chills or chilly sensations, headaches, night sweats and general malaise. Some patients are able to continue work for four or five days prior to hospitalization, while others are admitted in twenty-four to forty-eight hours with a temperature elevated to 102 to 104 F. Usually the pulse and respiratory rates are low in comparison to the fever, but an occasional patient is intensely dyspneic and even cyanotic. The fever usually subsides in three to five days by lysis. There is a normal leukocyte count early, and a secondary rise to 12,000 to 18,000 in a week to ten days.

The changes in the chest shown on physical examination are minimal in comparison to the extent of the disease shown roentgenographically. Often there are no abnormal conditions in the chest on admission, but after two or three days dulness over the affected site, impaired or decreased breath sounds and rales are noted. As the temperature falls, coarse rales are frequently noted to increase in numbers, and in many patients they first become noticeable during this period of defervescence. Rarely do patients show evidence of tubular breathing, as expected when there is pneumonic consolidation. There is often a great disproportion between the relatively mild clinical signs and symptoms and the roentgen observations. This suggests that the underlying process may be largely atelectatic rather than entirely infectious. Furthermore, the fact that frequently the roentgen changes precede the physical changes raises the question as to whether or not the original lesion is relatively minimal but sufficient to produce lobular atelectasis and whether the rales and impaired breath sounds later noted are secondary to the atelectasis.

Examinations of the sputum for the most part show only the normal inhabitants. Approximately 15 per cent of patients have bloody sputum. Rhoads¹¹ expressed the belief that *Streptococcus viridans*, which was present in most of his cases, contributed to the death of 1 patient. Others have considered that such organisms are secondary invaders and of no importance. Kneeland and Smetana¹² reported only the usual bacterial flora,

such as nonhemolytic streptococci, *Str. viridans*, *Staphylococcus albus*, *Staphylococcus aureus* and gram-negative cocci. Hemolytic streptococci and *Haemophilus influenzae* are inconspicuous. Occasionally higher types of pneumococci which cannot be typed are found. They stated that secondary bacterial infection of the lungs occurs rarely.

Others¹³ described a more severe and prolonged form of the disease occurring along with the milder forms in the same epidemic and in a few instances ending in death. The more severe form, as would be expected, shows more extensive pulmonary changes both on physical and on roentgen examination. The onset and course in this form are similar to those of the milder form for the first week or so. The patients then become more critically ill and have a severe cough, which is frequently productive. They are dyspneic, cyanotic and exhausted. The temperature is elevated from 104 to 105 F for a number of days. Continuous oxygen therapy and repeated transfusions are necessary. The pneumonia is usually bilateral and shows a tendency to migrate. The course is longer, and in some instances the disease persists for months.

Reimann^{8b} described the infection as spreading rapidly in some cases and more slowly in others until the trachea, bronchi and eventually the lungs are involved in a diffuse, bilateral process which persists for several weeks and is followed by a residuum lasting several months. There is involvement of much of the bronchiolar system as manifested by dyspnea and cyanosis, but consolidation is never striking. Kneeland and Smetana¹² described the presence of obstructed breathing which may be associated with areas of atelectasis. Some of their patients, they stated, gave the picture of extreme pulmonary insufficiency and were cyanotic even in high concentrations of oxygen. Recently in a review of 1,862 cases of atypical pneumonia by van Ravenswaay and

11 Rhoads, P. S. The Probable Incidence and Clinical Features of "Virus" Pneumonia, *Radiology* **40** 327-338 (April) 1943.

12 Kneeland, Y., and Smetana, H. F. Current Bronchopneumonia of Unusual Character and Undetermined Etiology, *Bull. Johns Hopkins Hosp.* **67** 229-268 (Oct.) 1940.

13 (a) Correll, H. L., and Cowan, I. I. Primary Atypical Pneumonia, *U. S. Nav. M. Bull.* **41** 981-987 (July) 1943. (b) Hufford, C. E., and Applebaum, A. A. Atypical Pneumonia of Probable Virus Origin, *Radiology* **40** 351-359 (April) 1943. (c) Longcope, W. T. Bronchopneumonia of Unknown Etiology (Variety X), *Bull. Johns Hopkins Hosp.* **67** 268-305 (Oct.) 1940. (d) van Ravenswaay, A. C., Erickson, G. C., Reh, E. P., Siekierski, J. M., Pottash, R. R., and Gumbiner, B. Clinical Aspects of Primary Atypical Pneumonia, *J. A. M. A.* **124** 1-6 (Jan. 1) 1944. (e) Reimann^{8b}. (f) Reimann, Havens and Price^{8c}. (g) Reimann^{8d}. (h) Smiley, Showacre, Lee and Ferris^{10e}. (i) Grieco, Cove and Klein^{10h}. (j) Kneeland and Smetana¹².

co-workers,^{13d} the increasing virulence of atypical pneumonia was stressed. Recurrence of the pneumonia in patients allowed up too soon was as high as 23.3 per cent. An additional 18.5 per cent had other complications, such as pleural fluid, empyema, chronic bronchitis and bronchiectasis.

Roentgen Observations—The roentgen signs of atypical pneumonia usually do not appear until the fourth day,^{10a} are less dense than are seen in

part of the chest but is most commonly seen in the right cardiophrenic angle. The mottled type of densities is interpreted as a lobular form of atelectasis based on a mechanical factor, the complete block of the smaller bronchi and bronchioles by exudate and swollen epithelium. Correll and Cowan^{13c} described two fairly frequent types: one in which the roentgenogram reveals a dense circumhilar shadow with a fanlike infiltration into the surrounding pulmonary tissue, and a



Fig 1—Roentgen varieties of proved atypical pneumonia. Bronchiectasis did not develop in these cases. *A*, streaking and mottled densities extending from the root of the lung down over the diaphragm, *B*, diffuse veil-like shadow involving the greater portion of the lower lobe of the right lung and mottled density in the left costophrenic sulcus, *C*, circumhilar shadow with fanlike infiltration into the surrounding pulmonary tissue, *D*, atelectasis of the lower lobe of the right lung associated with a mediastinal shift to that side in a case of atypical pneumonia.

cases of lobar pneumonia, and are described as following certain patterns (fig 1). In Campbell's¹⁴ series, the majority of the roentgenograms reveal streaking densities which radiate downward from the root of the lung and extend over the leaf of the diaphragm. Others show a mottled type of shadow which may occur in any

second, relatively frequent, type suggestive of atelectasis of a lobe, in that there is usually a diffuse veil-like shadow which occupies about two thirds of the lobe. Curtzweiler and Moore¹⁵ stated that in the circumhilar type a lateral projection frequently shows such lesions to be along the bronchus of the dorsal lobe rather than at

14 Campbell, T. A., Strong, P. S., Grier, G. S., and Lutz, R. J. Primary Atypical Pneumonia, *J. A. M. A.* 122: 723-729 (July 10) 1943.

15 Curtzweiler, F. C., and Moore, B. E. Primary Atypical Pneumonia of Unknown Etiology, *Radiology* 40: 347-350 (April) 1943.

the hilus. They contended that the involvement is always along the distribution of a portion of the bronchial tree. Haight and Trolinger^{10b} described four types: homogeneous, mottled, linear and a combination of the three. It was felt by them that the lesions usually retain their original appearance and do not spread or become confluent. This would suggest that the underlying lesion is mechanical (atelectasis) rather than wholly infectious (pneumonia). In contradistinction, Dingle and associates^{10c} commented on the rapidity of the change in the roentgen appearance of the lesions over a period of a few days. Other observers¹⁶ described the pneumonia as migratory. New foci of pneumonic infiltration may develop rapidly in other lobes and in the opposite lung. Multiplicity of lobes involved is reported in 10 to 20 per cent of cases. McCarthy^{10a} and Campbell¹⁴ described as one of the roentgen varieties parenchymal areas of infiltration resembling tuberculosis.

Pathologic Aspects—Deaths from this disease are rare, consequently pathologic data are scarce. Most of the patients in whom death occurred died as a result of preexisting complicating heart and kidney diseases. The significant pathologic findings in the reported deaths will be summarized.

Kneeland and Smetana¹² reported 1 death in 52 cases. The microscopic appearance of the lungs showed occasional septums to be thickened by fibrous tissue and infiltrations consisting of mononuclear wandering cells and polymorphonuclear leukocytes. Some alveoli showed large mononuclear cells arranged in rows about the periphery. An occasional hyaline membrane was present. The mucosa of the larger bronchi and of the trachea was densely infiltrated by polymorphonuclear leukocytes and mononuclear wandering cells. Their epithelial lining cells were prominent and frequently projected into the lumens in the form of small papillae. Some of the lumens contained mucopurulent exudate and debris. In summary, the alveoli, interstitium and bronchi were the areas affected by this disease. The anatomic diagnosis was lobular pneumonia with organization and acute tracheo-bronchitis.

One death occurred in the 285 cases reported by Dingle and associates^{10c}. Microscopically, the lungs showed congestion and infiltration of the alveolar walls with monocytes, lymphocytes,

plasma cells and occasional neutrophils. A similar reaction was present in the perivascular and peribronchial interstitial tissues. The alveoli contained many large actively phagocytic monocytes, a moderate number of eosinophils, a scant number of neutrophils, fibrin, edema fluid and erythrocytes. The walls of the bronchi showed an acute inflammatory process with extensive ulceration of the bronchial mucosa, the lumens of the bronchi were plugged with an exudate composed chiefly of neutrophils. The conditions found were a hemorrhagic interstitial broncho-pneumonia and an acute ulcerative bronchitis.

Campbell and co-workers¹⁴ described 1 death among 200 patients. The microscopic examination revealed in the lungs bronchitis, bronchiolitis, peribronchitis and interstitial pneumonitis, and atelectasis secondary to the bronchiolitis and peribronchiolitis. The major bronchi showed sloughing of the epithelium. The mucosa was moderately edematous and diffusely infiltrated with lymphocytes, occasional plasma cells and a moderate number of neutrophils. The smaller bronchi showed a similar process with the lumens partly occluded by a purulent exudate. There was a conspicuous peribronchial accumulation of lymphocytes and plasma cells. There was a general decrease in the size of the alveoli. This process was associated frequently but not always with a thickening of the alveolar wall. The alveoli with thickened walls contained numerous cells. Many of the alveoli were atelectatic as a result of the bronchial plugs.

Longcope^{13c} reported 32 cases of atypical pneumonia with 2 deaths. Both of these occurred in patients with preexisting chronic rheumatic heart disease. Microscopically the lungs showed the bronchi to be filled everywhere with a thick exudate consisting of about half polymorphonuclear leukocytes and half round cells. Their walls were everywhere infiltrated with round cells and occasional polymorphonuclear leukocytes. All the alveoli were solidly filled with round cells. There was almost complete absence of polymorphonuclear leukocytes everywhere except in the bronchi in 1 case, while in the other the peribronchial alveoli were similarly involved. The bronchial epithelium of the larger bronchi showed squamous metaplasia.

The pathologic changes of the patients dying from atypical pneumonia as described by McCarthy,^{10a} Rhoads¹¹ and Saphir¹⁷ were similar in most respects to those in preceding pathologic reports except that the interstitial nature of the

16 Haight and Trolinger^{10b}, Rhoads¹¹, Kneeland and Smetana¹², Campbell, Strong, Grier and Lutz¹⁴, Correll and Cowan^{13a}, Hufford and Applebaum^{13b}, Longcope^{13c}.

17 Saphir, O. Pathological Changes in Atypical Pneumonia, *Radiology* 40: 339-343 (April) 1943.

process was more apparent than the evidence of bronchial and bronchiolar infection

Adams¹⁸ discussed the pathologic observations on 9 infants dying during an epidemic of 32 cases of viral pneumonia. Grossly, the pulmonary tissue was congested, with scattered areas of hemorrhagic bronchopneumonia. Exudate could be expressed from the bronchi and bronchioles. Microscopically, the outstanding pathologic features were necrosis and ulceration of the bronchial epithelium with a rather high degree of atelectasis in all cases. The bronchial and bronchiolar lumens were filled with sloughed epithelial cells. Patches of peribronchial infiltration were composed mainly of mononuclear cells. The edema, hemorrhage and swelling of the surrounding parenchymal tissues seemed to contribute to the collapse of the bronchiolar system. Polymorphonuclear leukocytes, lymphocytes and large mononuclear phagocytes were found in the alveolar spaces. Characteristic cytoplasmic inclusion bodies were found in the bronchial epithelium in all fatal cases occurring in this epidemic.

In summary, it is noted that clinically, roentgenologically and pathologically atypical pneumonia may present two factors commonly described in the pathogenesis of bronchiectasis, namely, bronchial and bronchiolar infection and occlusion as well as the more commonly recognized condition of interstitial pneumonitis. The bronchial occlusion, as manifested by areas of atelectasis, is demonstrated microscopically by the swollen, edematous and ulcerated mucous membrane and bronchial plugs of purulent exudate. The atelectatic feature of atypical pneumonia is demonstrated in the roentgenogram presented in figure 1 D.

THE ROLE OF BRONCHIAL OBSTRUCTION AND INFECTION IN THE PRODUCTION OF BRONCHIECTASIS

Many theories have been advanced regarding the cause and pathogenesis of bronchiectasis. Some authors still emphasize the congenital nature of the disease, but the majority at the present time believe that bronchiectasis is acquired. The correlation between bronchial infection and obstruction with resulting atelectasis, and the subsequent development of bronchiectasis as demonstrated by careful analysis of case records, serial roentgenograms and postmortem examinations has suggested this pathogenesis.

18 Adams, J. M. Primary Virus Pneumonitis with Cytoplasmic Inclusion Bodies, *J. A. M. A.* **116**: 925-933 (March 8) 1941.

This relationship was first noted in cases of foreign bodies present in the bronchial tree.

Anspach¹⁹ was among the first to stress the fact that an unrelieved basal triangular shadow indicative of atelectasis following bronchopneumonia in infants is important in the production of bronchiectasis. He added that only too often the patient is discharged from the hospital before the roentgen conditions have cleared or before additional roentgenograms have been taken, even though the temperature is essentially normal. He stated that in infants a collapsed lower lobe that remains atelectatic will reveal some evidence of bronchial dilatation within six weeks to two months. Anspach^{19b} was able to follow 100 consecutive patients presenting a small basal triangular roentgen shadow, the majority for a number of years. Eleven died and came to necropsy. Nine of these deaths occurred in infancy, within a few weeks after the first pulmonary symptoms. From necropsy studies and also as a result of following other patients with serial roentgenograms over a period of years, he stated that it is the bronchial or bronchiolar obstruction with resulting atelectasis that accounts for the triangular shadow and that under certain conditions it may be the precursor of the bronchiectasis and not merely an associated finding.

Tannenberg and Pinner,²⁰ in an attempt to clarify the causative role that bronchial obstruction plays in the development of bronchiectasis, performed a number of animal experiments, producing bronchial obstruction by intrabronchial and extrabronchial methods. Simultaneously, in part of the experiments a pneumothorax on the operative side was produced, to determine whether or not the loss of the usually high negative intrapleural pressure encountered in atelectasis was the actual force causing the bronchi to dilate. Definite evidence of bronchial dilatation and saccular bronchiectasis with roentgen evidence of atelectasis were found in rabbits dying not earlier than two weeks after the operation. The most extensive bronchiectasis was noted in rabbits which died between the twenty-fifth and the thir-

19 Anspach, W. E. (a) Atelectasis and Bronchiectasis in Children. A Study of Fifty Cases Presenting a Triangular Shadow at the Base of the Lung, *Am. J. Dis. Child.* **47**: 1011-1051 (May) 1934, (b) Bronchiectasis, Collapsed Lung, and the Triangular Basal Shadow in the Roentgenogram, and Their Inter-Relationship, *Am. J. Roentgenol.* **41**: 173-183 (Feb.) 1939, (c) Roentgenologic Aspects of Bronchiectasis, *Dis. of Chest* **9**: 24-38 (Jan.) 1943.

20 Tannenberg, J., and Pinner, M. Atelectasis and Bronchiectasis. An Experimental Study Concerning Their Relationship, *J. Thoracic Surg.* **11**: 571-616 (Aug.) 1942.

tieth postoperative day. The presence and maintenance of a pneumothorax on the obstructed side did not essentially alter the final result, it did not prevent the formation of bronchiectasis. "Death of many of the rabbits was caused apparently by a contralateral bronchopneumonia, probably the result of intrabronchial aspiration of exudate from the bronchiectatic lung," but such areas of bronchopneumonia when uncomplicated by bronchial obstruction never became bronchiectatic. Similarly, when the bronchial obstruction was not associated with bronchial infection distal to the point of obstruction or when the obstruction had not become complete, as a result of a localized area of bronchial dilatation at the site of the obstructing agent sufficient to allow bronchial drainage, bronchiectasis did not result. These experiments suggest that bronchial

seen in whom symptoms suggestive of bronchiectasis develop following a protracted course of atypical pneumonia, this cause and effect relationship should be considered.

In an attempt to determine the permanency and extent of the bronchial and bronchiolar damage in the 20 cases of bronchiectasis attributable to atypical pneumonia, bronchography was repeated over a period of two to six months. In only 3 instances in this small series were bronchiectatic bronchi noted to resume their normal contour and show evidence of clearing (fig 2). The bronchiectasis in the remaining 17 patients appeared to be permanent. Because of persistent clinical symptoms as well as bronchographic evidence of bronchiectasis, 10 of these 17 patients have had lobectomies. The interval between the acute episode of atypical pneumonia and the

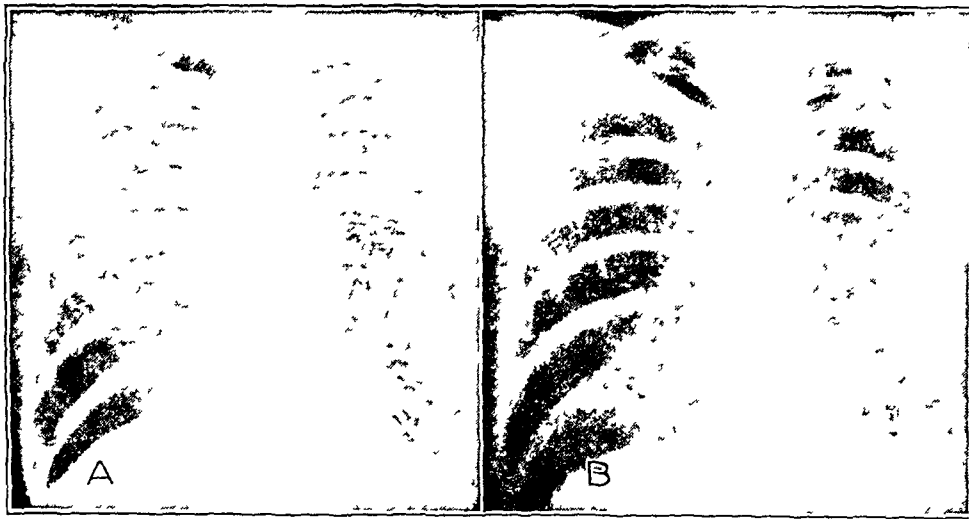


Fig 2—Reversible bronchiectasis in a patient with atypical pneumonia in September 1943 and again in January 1944. Because of symptoms suggestive of bronchiectasis, bronchograms were made on March 15 (A), which revealed cylindric bronchiectasis confined primarily to the larger bronchi. After clinical improvement during the next four months bronchography was repeated on July 1 (B), revealing no bronchiectasis. A bronchogram of the right side was normal.

obstruction and infection are both necessary in the development of bronchiectasis. A coexisting pneumothorax did not alter the result. This confirms Andrus'²¹ previous experiments and his assertion that increased negative pressure of the pleural space does not exert any significant dilating stress in the presence of atelectasis.

RELATIONSHIP OF ATYPICAL PNEUMONIA TO BRONCHIECTASIS

So far it has been shown that bronchial and bronchiolar infection and occlusion may occur in atypical pneumonia. Furthermore, other authors have shown both clinically and experimentally that these two factors may produce bronchiectasis. Therefore, when a number of patients have been

operation varied from six to thirteen months. As will be noted later in the case presentations, there was pathologic verification of the irreparable bronchiectatic damage to the bronchial tree in the lobes resected, substantiating the permanency of the bronchial destruction by the previous disease process. Blades and Dugan²² have reported pseudobronchiectasis following atypical pneumonia which cleared spontaneously within two to three months of the acute disease. Reversible bronchiectasis (pseudobronchiectasis) as noted in my 3 cases may occur if the bronchial and bronchiolar destruction produced by the disease process has not been sufficient to produce irreparable damage to the bronchial walls. All gradations of bronchial and bronchiolar damage

²¹ Andrus P M. Bronchiectasis. An Analysis of Its Causes, *Am Rev Tuberc* 36 46-79 (July) 1937.

²² Blades, B, and Dugan D J. Pseudobronchiectasis Following Atypical Pneumonia, *Bull U S Army M Dept*, November 1943, no 70, pp 60-68.

may result, depending on the severity and the duration of the disease process. Bronchographically such bronchial dilatation is usually cylindrical and confined to the larger bronchi. Only repeated bronchographic examinations over a period of months will determine when bronchiectasis is permanent and when it is reversible. The decision as to operation should be postponed until an established diagnosis is made.

essentially uncomplicated. The abnormal roentgen conditions in this group had completely disappeared prior to bronchography in all but 2 cases. Except in these 2 cases the bronchograms were normal. These 2 cases are examples of less severe bronchial damage resulting from atypical pneumonia and might be considered as intermediate stages in the development of bronchiectasis.

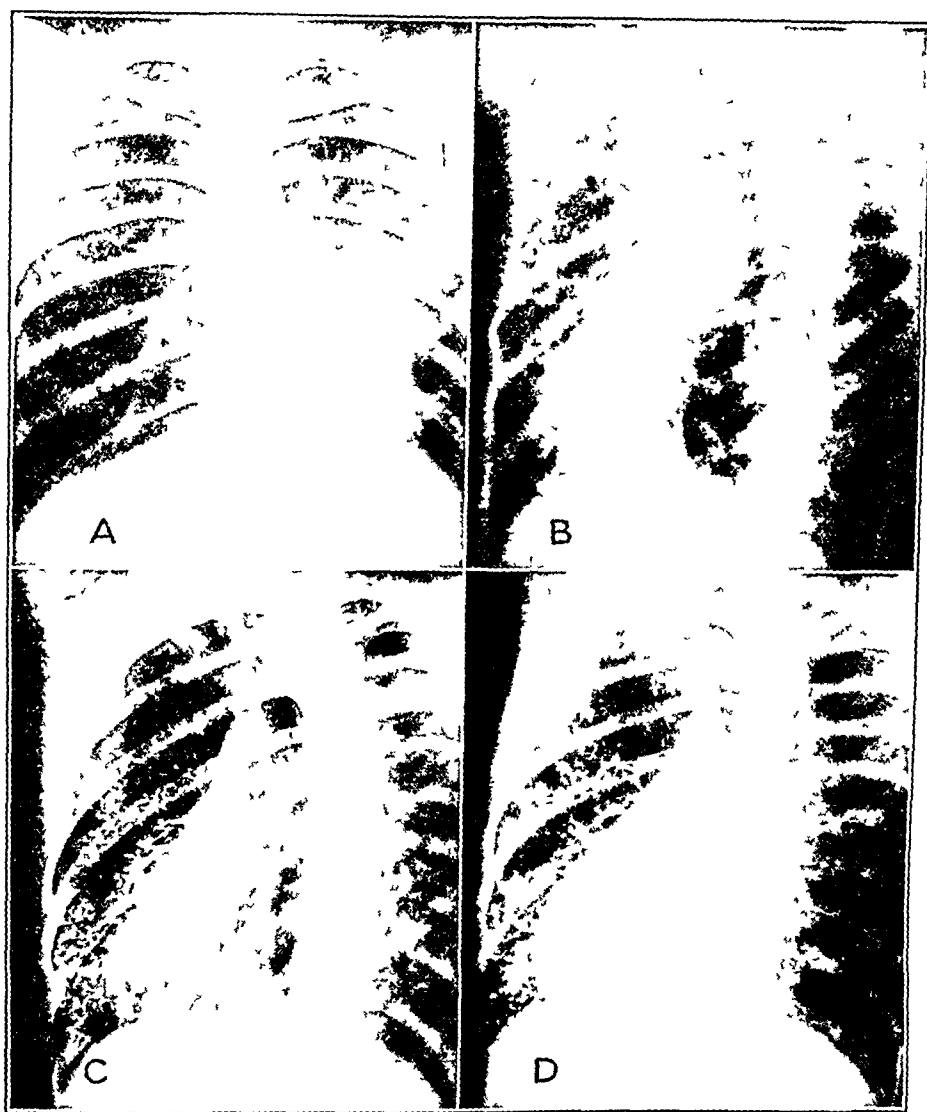


Fig 3—Roentgenogram and serial bronchograms over a period of four months of a patient having atypical pneumonia in which the roentgen and physical abnormalities persisted over a longer period than usually noted. *A*, roentgenogram demonstrating a residual pneumonitis in the lingula of the left lung, the site of involvement by atypical pneumonia, *B*, a right anterior oblique bronchogram demonstrating the bronchi of the lingula to be slightly dilated and more closely crowded together and to have blunted ends—probably indicative of inspissated exudate in an atelectatic lingula, *C* and *D*, serial right anterior oblique bronchograms over a four month period demonstrating gradual return to normal of the lingular bronchial tree and filling by iodized poppyseed oil of this bronchial segment. Physical abnormalities also disappeared at this time.

Bronchographic examinations were performed on 15 additional patients who had had atypical or viral pneumonia from one to four months previously. In some of these patients the course of the atypical pneumonia had been somewhat protracted, rales had persisted or there had been roentgen evidence of atelectasis or unresolved pneumonia for some time. In the majority of these cases, however, the course had been

The first patient was an 18 year old white youth who was hospitalized July 5, 1943 for atypical pneumonia. The temperature on admission was 103 F, and the white blood cell count was 8,000. Roentgenograms taken two days after admission showed pneumonitis extending out from the left hilus (fig 3 *A*), but rales were not heard until after one week. The temperature became normal within a week and the patient felt considerably better, but a nonproductive cough persisted for about two months, associated with weakness and loss of weight. Rales could be heard during this time.

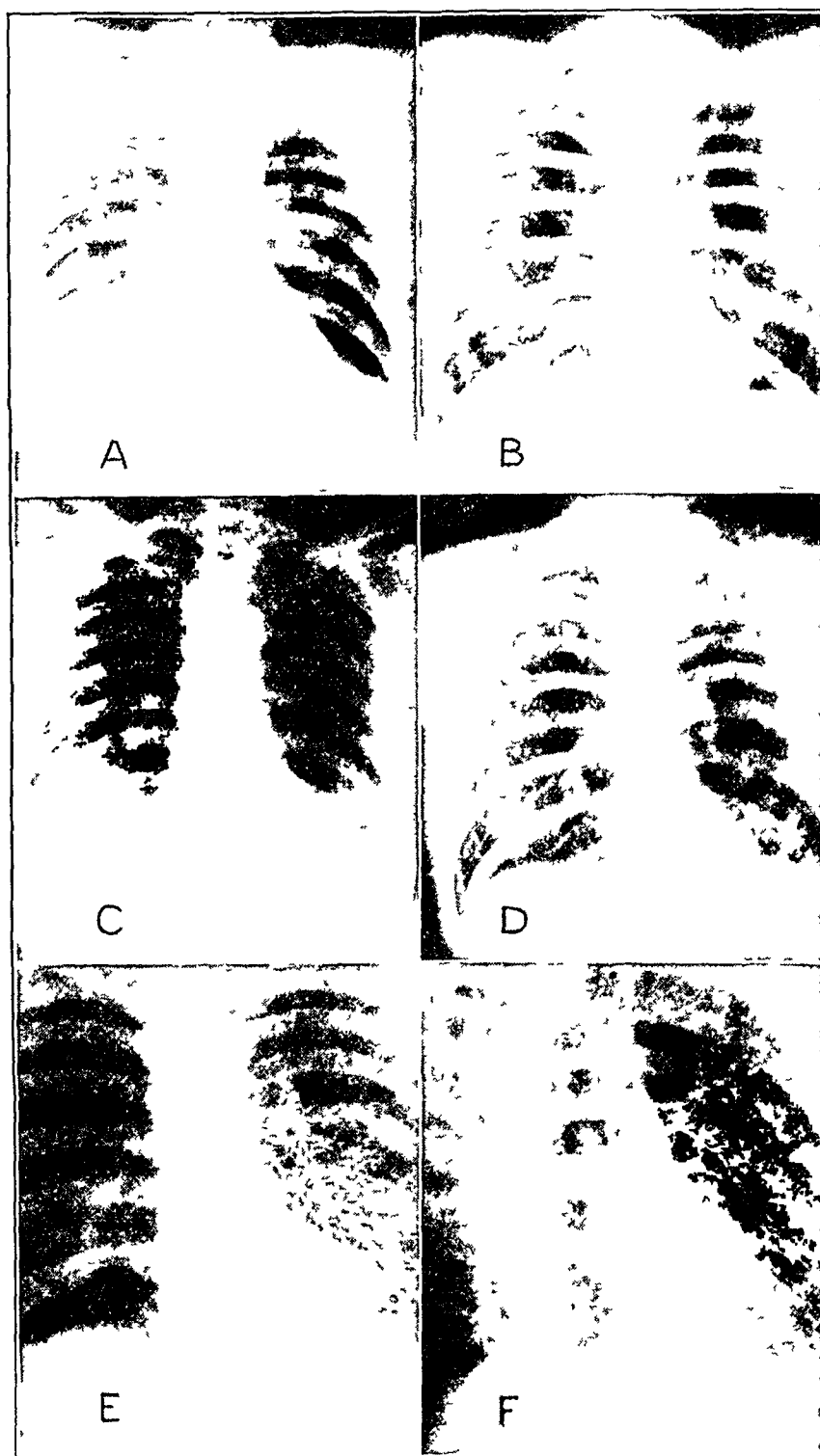


Fig 4—Serial roentgenograms and bronchograms of a patient having atypical pneumonia persisting over a longer period than usually noted and giving rise to damaged, dilated and distorted bronchi and bronchioli of the lower lobe of the left lung. *A*, roentgenogram demonstrating elevation of the right side of the diaphragm associated with atelectasis of the lower lobe of the right lung during an acute episode of atypical pneumonia. *B*, roentgenogram showing spontaneous improvement of the atelectasis within one week. There is also noted roentgen evidence of pneumonitis in the lower lobe of the left lung and beginning obliterative pleuritis of the left costophrenic gutter. *C*, a roentgenogram one month later demonstrating a recurrence of the atelectasis of the right lower lobe with elevation of the right side of the diaphragm. Again, there was spontaneous improvement within one week's time. There was increase in the pneumonitis of the left lower lobe over that noted in the roentgenogram one month previously (*B*). *D*, persistence of the pneumonitis of the left lower lobe for an additional month. The right side had remained clear. *E*, bronchogram demonstrating evidence of bronchial and bronchiolar damage, dilatation and distortion by the pneumonic process. Additional bronchograms revealed the right bronchial tree to be normal. *F*, right anterior oblique bronchogram repeated after a seven week interval demonstrating slight increase in the bronchial dilatation. Additional bronchograms will subsequently be obtained to see whether this process is progressive, stationary or reversible.

over the lingular area. Serial roentgenograms revealed unresolved pneumonia and a questionable atelectasis of the lingula for a period of several months. The initial bronchogram (fig 3B) demonstrated an atelectatic lingula with dilated bronchi that were crowded together and had blunted ends—probably a result of inspissated exudate. Repeated bronchograms over the next four months showed gradual clearing (fig 3C and D). If the bronchial occlusion and atelectasis had persisted in this case, bronchiectasis might have resulted.

The second patient was a 51 year old officer who was hospitalized for two weeks in November 1943 for atypical pneumonia. The past history was entirely noncontributory. His clinical course was typical for atypical pneumonia in all respects except that there were few symptoms referable to the lungs. A roentgenogram of the chest taken on November 9 showed massive atelectasis of the lower lobe of the right lung with an elevated diaphragm and mediastinal shift (fig 4A). By November 16, there had been spontaneous clearing of the lobar atelectasis (fig 4B), but as noted in this roentgenogram there was a beginning obliterative pleuritis on the left side. Still there were no significant symptoms referable to the chest proper. The patient was returned to duty and felt entirely well until December 19, at which time there was a recurrence of symptoms. There was a severe cough productive of 4 to 5 ounces (120 to 150 cc) of purulent sputum daily and an elevation of temperature to 104 F for four days that gradually fell by lysis. The patient was again hospitalized, and again massive atelectasis of the right lower lobe was noted (fig 4C). As before, there was spontaneous clearing of the atelectasis within a week. However, a new pneumonic process was noted in the base of the lower lobe of the left lung in the roentgenograms taken December 19. Also there was an increase in the obliterative pleuritis, resulting in an elevation and flattening of the diaphragm on the left side. This process in the left lower lobe persisted for the next month (fig 4D) associated with basilar rales on this side. However, the productive cough disappeared. The patient then transferred to Percy Jones General Hospital. Bronchoscopic examination performed Jan 24, 1944 showed an erythematous granular mucous membrane with several small superficial areas of ulceration in the bronchus of the lower lobe of the left lung, while the bronchus of the lower lobe of the right lung showed rather extensive ulceration of an acute nature with some diminution of the bronchial lumen. Because of the suggestive evidence of bronchiectasis, bronchograms were taken on January 31. Damaged, dilated and somewhat distorted bronchi and bronchioles as noted in the bronchograms (fig 4E) were found. The progressive obliterative pleuritis and the distortion and dilatation of the bronchi of the lower lobe of the left lung over a period of two months as noted roentgenologically suggested that the underlying process might still be active. This probably resulted from a combination of bronchial destruction and an interstitial fibrosis. The patient was reexamined bronchoscopically on March 11, and complete healing of the previous ulcerative bronchitis was noted, however, bronchographic examination on March 21 (fig 4F) showed a slight increase in the bronchial dilatation. Subsequent bronchograms will be obtained later to determine whether this process is stationary, progressive or reversible.

Representative cases of patients acquiring bronchiectasis following attacks of so-called atypical pneumonia will now be presented. As pre-

viously stated, these patients were entirely free from pulmonary symptoms prior to the pneumonia—the roentgenograms taken at the time of their induction into the Army were normal. The symptoms and signs of the acute phase were typical in every respect, but the subsequent courses were either protracted or recurrent. The majority of the patients had multiple lobar involvement. The initial sites of the pneumonia were not always the areas later found to have become bronchiectatic. Rales and roentgen evidence of unresolved pneumonia persisted. A productive cough developed, and after several months bronchographic examinations revealed the presence of bronchiectasis. Repeated bronchograms in this group showed that the bronchiectasis was irreversible. This was further confirmed by the microscopic examination of the resected lobes.

CASE 1—This patient was a 31 year old white man who was hospitalized on Jan 24, 1943 for a cold in the head and chest characterized by a temperature of 102 F, a dry cough, sore throat and general malaise. The past history was noncontributory. Prior to the present illness the patient had always been in the best of health. He had been a champion tennis player and had played trumpet in a band. During early childhood he had had both measles and whooping cough without complications. The induction roentgenogram (fig 5A) was normal. The physical examination revealed rales and diminished breath sounds at the base of both lungs. The white blood cell count was normal. Unfortunately, no roentgenograms of the chest were taken during this hospitalization. The temperature gradually returned to normal in three days, and the patient was returned to duty in five days. During the latter part of February 1943 he again noted a pharyngitis and tracheobronchitis which was associated with cough and increasing amounts of purulent sputum. This increased over a period of two to three months, but he continued duty. He lost about 20 pounds (9 Kg) in weight during this period. Not until he had an acute exacerbation associated with chills did he seek medical attention. He was hospitalized on May 20, with a temperature of 103.5 F and an elevation of leukocytes to 20,000. Physical examination at this time showed diminished breath sounds, dullness and rales at the base of both lungs posteriorly. Serial roentgenograms during the following three months showed multiple foci of bronchopneumonia in both the right and the left lung (fig 5B). After approximately one month, however, all but the basilar involvement showed resolution (fig 5C). Because of basilar pneumonitis, the persistent physical findings and the presence of a productive cough, bronchiectasis was suspected. Bronchograms were made August 9, which confirmed the clinical impression of bronchiectasis (fig 5D). The patient was then transferred to Percy Jones General Hospital. Six weeks later bronchography was repeated, and again there was revealed the presence of extensive cylindric and saccular bronchiectasis bilaterally. With conservative therapy the symptoms of bronchiectasis remained unabated over the next several months. A lobectomy of the lower lobe of the left lung was performed on November 10. The postoperative course was uneventful. Microscopically, sections of the removed lung

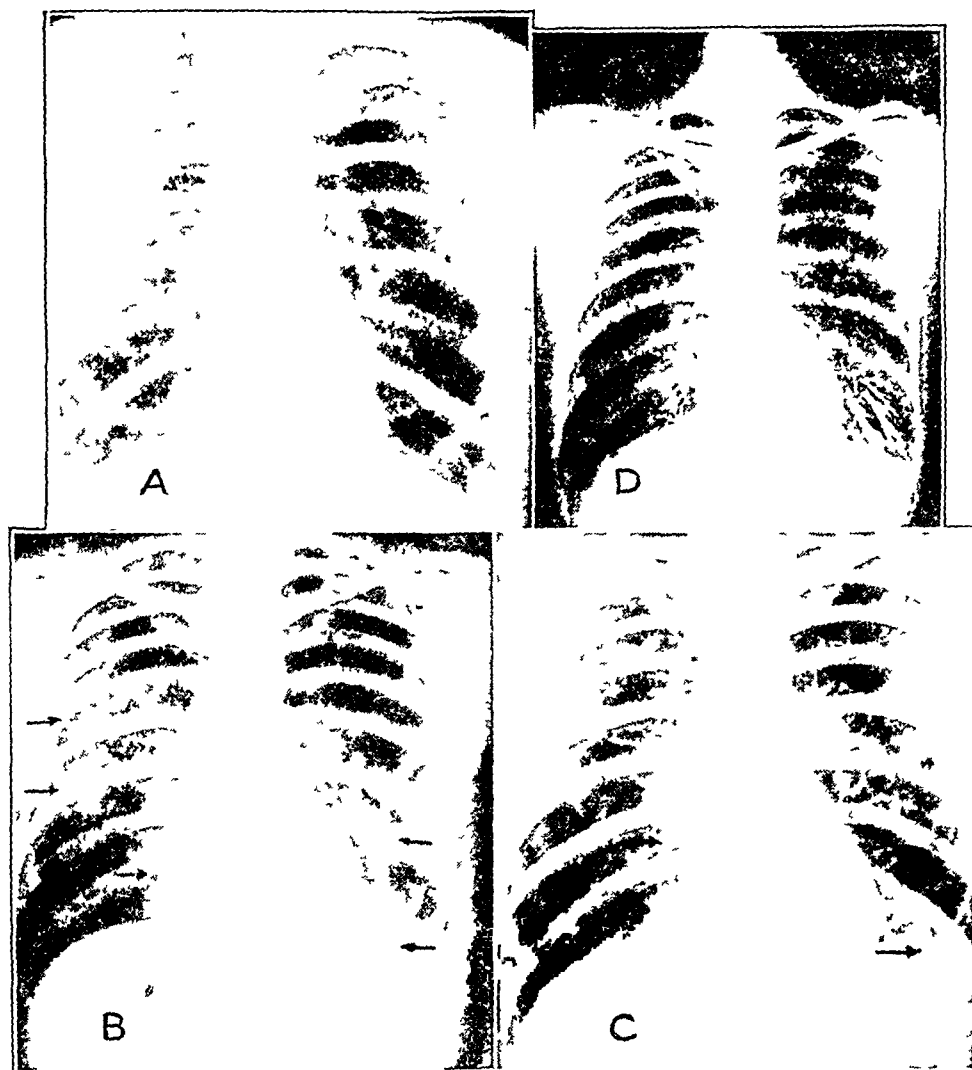


Fig 5 (case 1) —Roentgenograms demonstrating the development of bronchiectasis in a case of atypical pneumonia. *A*, roentgenogram of a healthy chest at the time of induction into the Army. *B*, roentgenogram taken during the acute illness of atypical pneumonia, demonstrating the multiple foci of pneumonic involvement. *C*, roentgenogram taken one month after *B*, demonstrating persistence of the pneumonia at the right cardiophrenic angle and the base of the left lung. Evidence of unresolved pneumonia remained in these areas. *D*, bronchograms made prior to the patient's transfer to this hospital, demonstrating the development of bilateral basilar bronchiectasis at the sites previously illustrated as showing evidence of failure to resolve. Subsequent bronchograms showed no change in the degree of bronchiectasis.

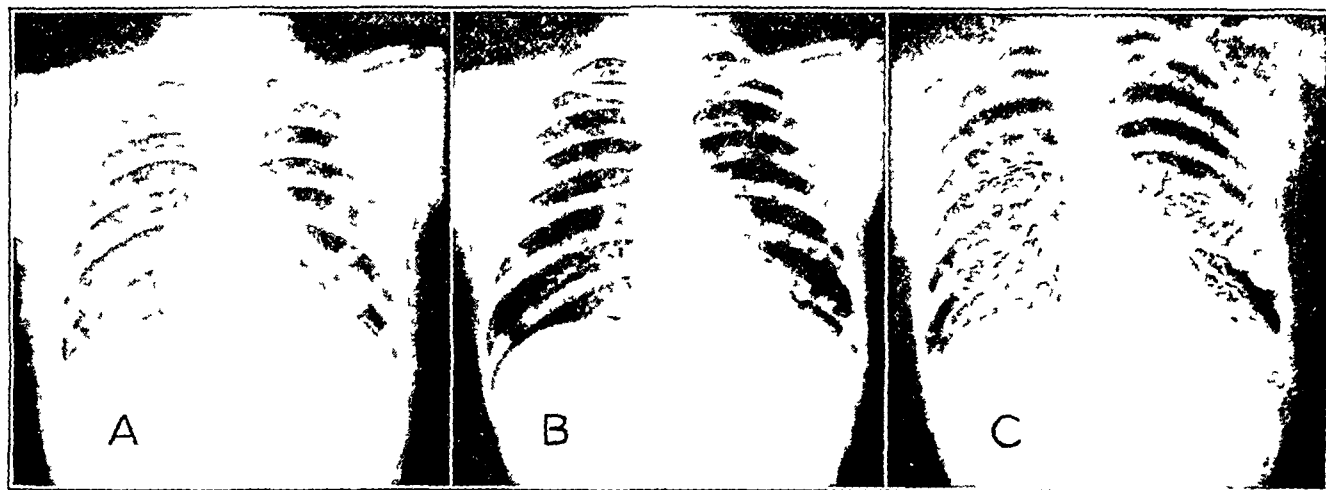


Fig 6 (case 2) —Roentgenograms demonstrating the development of bronchiectasis in a case of atypical pneumonia. *A*, roentgenogram taken Feb 12, 1943, demonstrating a new focus of pneumonia at the right cardiophrenic angle and a recurrence of the pneumonia at the base of the left lung. *B*, roentgenogram taken four months after the previous one, demonstrating the persistence of pneumonitis at the base of the left lung. *C*, bronchogram made Aug 20, 1943, demonstrating the development of bronchiectasis at the previous site of unresolved pneumonia. Subsequent bronchograms showed no change.

tissue showed greatly dilated bronchi and bronchioles. There was pronounced inflammatory thickening of their walls and of the surrounding parenchyma. The lumens contained a purulent exudate. The epithelial lining was infiltrated with polymorphonuclear leukocytes. The muscularis could scarcely be identified as such except for short fragments of degenerated fibers. The connective tissue support was similarly incomplete, variable in amount and hyalinized. The largest component of the wall appeared to be the granulomatous infiltration. The peribronchial alveoli were atelectatic and densely infiltrated with lymphocytes and histiocytes. Many of the alveolar lumens were obliterated, and others were filled with a purulent exudate.

The white blood cell count on admission was 5,100, but in six days it became elevated to 27,900 and gradually subsided to normal over a period of two weeks. The temperature dropped to normal within seventy-two hours. The initial roentgenogram, on February 3, showed mottled densities in the lower lobe of the left lung suggestive of atypical pneumonia. By February 10, the chest was reported as clear roentgenologically, but within two days there was evidence of a new pneumonic process at the right cardiophrenic angle (fig 6A) as well as recurrence in the base of the left lung. The patient at this time clinically had an exacerbation of his illness, with a temperature of 104 F for several days. The roentgen examination on February 25 again

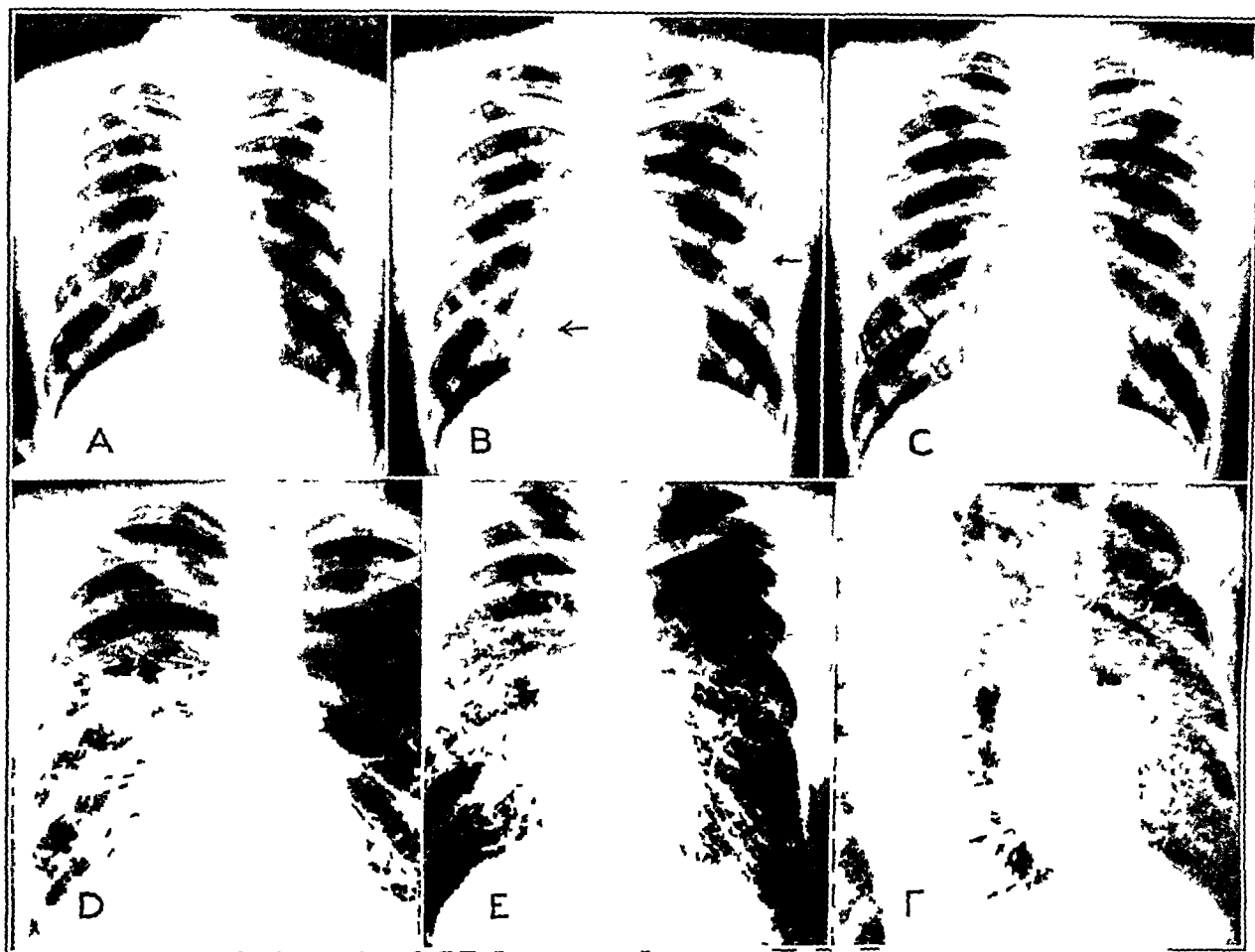


Fig 7 (case 3)—Roentgenograms demonstrating the development of bronchiectasis in a case of atypical pneumonia. A, healthy chest at the time of induction into the Army. B, multiple foci of pneumonic involvement. C, clearing of the pneumonia in the left pulmonary field but persistence over a period of several months at the right cardiophrenic angle, with some evidence of atelectasis at this site. D, E and F, serial bronchograms over a period of four months, demonstrating no change in the degree of bronchiectasis of the lower lobe of the right lung.

CASE 2—This patient was a 21 year old white man. The past history was noncontributory except that during early childhood he had had measles, mumps, chickenpox, whooping cough and scarlet fever. He had had no pulmonary complaints prior to the onset of the present illness. The induction roentgenogram showed normal pulmonary conditions. About the middle of January 1943 he contracted a cold in the chest characterized by an unproductive cough, sore throat, fever and night sweats. After three weeks the temperature suddenly rose to 104.4 F. He was hospitalized on February 2, and an initial diagnosis of atypical pneumonia of the lower lobe of the left lung was made. Examination showed slightly impaired breath sounds and fine moist rales at the base of the left lung posteriorly.

showed pneumonia at the base of the left lung, and the patient continued to have impaired breath sounds and rales at the base of this lung posteriorly up to the time of discharge from the hospital on March 3. He felt well generally, but about April 1 he began coughing and raising increasing amounts of greenish yellow purulent sputum. He now complained of general debility, and his weight dropped from 146 to 120 pounds (66.2 to 54.4 Kg). On May 30 he again had a flare-up of the pulmonary symptoms characterized by dull pain in the left side of the chest, fever and a more pronounced productive cough. He was again hospitalized. The temperature remained around 100 F for several days, and the white blood cell count was 12,600. Roentgenograms taken on June 5 again showed the

pneumonic process at the base of the left lung (fig 6 B). The patient was then transferred to Percy Jones General Hospital. Bronchograms taken on August 20 showed bronchiectasis of the lower lobe of the left lung (fig 6 C). Bronchoscopic and postural drainage gave the patient temporary relief from the chronic cough and sputum, but the symptoms soon recurred. Consequently, after it was determined that the patient's symptoms of bronchiectasis were not going to be relieved by conservative management, a lobectomy of the lower lobe of the left lung was performed on November 19. The pathologic sections of the resected pulmonary tissue revealed severe chronic inflammation of the bronchi and peribronchial tissues. There were irregular, wide, branching dilatations of the bronchial lumens and formation of numerous polypoid projections of inflamed mucosa extending into them. More deeply there was complete destruction of the muscularis and replacement by fibrous scar tissue infiltrated with lymphocytes, plasma cells, histiocytes and some eosinophils. The peribronchial alveoli were atelectatic, and their septums were moderately infiltrated in the same manner as the bronchi.

CASE 3—This patient was a 22 year old white man who in February 1943 contracted a cold in the chest associated with fever, general malaise and a productive cough. The past history was entirely noncontributory except for the fact that fourteen teeth had been extracted during the preceding six months under local anesthesia. The induction roentgenogram (fig 7 A) was normal. There was no evidence roentgenologically or bronchoscopically of the presence of a foreign body causing bronchial obstruction. The symptoms were not severe enough for him to seek medical attention. During the next two months he had a moderate cough and raised variable amounts of sputum. Some days there would be none. The cough was worse when he was lying down and particularly at night. The appetite became poor, and the patient lost weight. He was hospitalized on April 23, 1943. The white blood cell count on admission was 10,300. Physical examination showed rales and slightly impaired breath sounds at the base of both lungs. The temperature was elevated to around 100 F daily for several weeks. A roentgen examination April 28 showed bilateral pneumonia (fig 7 B), particularly at the right cardiophrenic angle. After several weeks the left side of the chest cleared, but varying degrees of pneumonitis and atelectasis persisted at the right cardiophrenic border for the next four months (fig 7 C). After three weeks' hospitalization the cough and sputum greatly diminished. On June 14 a small hemoptysis occurred. Because of the persistent roentgen evidence of pneumonitis and the chronic productive cough the patient was transferred to Percy Jones General Hospital on August 15. Bronchograms made on August 20 showed bronchiectasis of the lower lobe of the right lung (fig 7 B). The left lung showed normal bronchial markings. During the latter part of August the patient had an acute exacerbation of his bronchiectasis, characterized by a temperature of 102 F and a pronounced increase in the cough and purulent sputum. The patient had a bronchoscopic examination at this time. A purulent exudate covered the mucosal surface of the right main stem bronchus. The mucous membrane was swollen and inflamed, particularly about the secondary orifices of the bronchus of the lower lobe of the right lung, causing partial obstruction. The mucous membrane about the orifices was thoroughly sponged with a solution of tetracaine and epinephrine hydrochloride. After bronchoscopic drainage, the sputum increased for sev-

eral days and then practically disappeared. For the past four months this patient has been entirely asymptomatic. In order to determine whether the bronchiectasis might have cleared, bronchography was repeated on two occasions over a period of four months. No change in the degree of bronchiectasis was noted, as demonstrated in the bronchograms (fig 7 E and F). This patient is probably in a dry phase of the bronchiectasis, a period during which infection and resulting sputum are at a minimum. Because of the complete absence of signs and symptoms, lobectomy has been postponed.

CASE 4—The patient was a 19 year old white youth whose past history was entirely noncontributory. There had been no childhood diseases and no previous attacks of pneumonia. The induction roentgenograms were normal. On Feb 8, 1943 there developed an acute nasopharyngitis and laryngitis with a temperature of 103 F. The white blood cell count was 6,700. Physical examination showed impaired breath sounds in the base of the left lung posteriorly and occasional rales. Roentgenograms were not taken until February 22, and by this time the chest was clear roentgenologically. The patient was discharged to duty on February 26, but he continued to cough and on March 3 a left pleural pain developed. He was again hospitalized, on March 7. The temperature was elevated to 100 F for several days and then not over an occasional 99 F for the next several months. Physical examination of the chest at this time revealed rales and a friction rub at the base of the left lung. Roentgenograms taken on March 8 showed pneumonia at the base of this lung. Subsequent roentgenograms showed a definite shift of the mediastinum to the left and a question of a triangular shadow at the left cardiophrenic angle. During this hospitalization the cough became severe and was productive of increasing amounts of purulent sputum, up to 4 to 5 ounces (120 to 150 cc) daily. On May 17 bronchograms revealed extensive tubular bronchiectasis in the lower lobe of the left lung. The patient was then transferred to Percy Jones General Hospital. Bronchographic examination was repeated June 8 and showed no improvement in the bronchiectasis. During this period the patient's cough, sputum and general condition became progressively worse. A lobectomy was performed on the lower lobe of the left lung on July 27. The pathologic examination revealed a diffuse process involving the bronchi and alveoli. The bronchial epithelium was pseudostratified and lay on a loose stroma of edematous granulation tissue. The bronchial musculature was almost entirely destroyed. A few remaining scattered islands of cartilage were noted, but the normal architecture had been totally altered. Occasional focal deposits of lymphoid tissue were seen in the bronchial submucosa. The outer wall of these dilated bronchi lay immediately against the parenchyma. The alveolar parenchyma was considerably reduced in volume by the interstitial fibrosis and the dilated bronchi and by atelectasis which was generally severe, leading to nearby complete airlessness. The alveolar lumens in general were either greatly contracted or filled with desquamated epithelium. The interstitial process was both fibrous and lymphohistiocytic.

CASE 5—The patient was a 21 year old white man. Except for rubella and the usual number of colds, his past history was entirely noncontributory. The induction roentgenogram was normal. On January 19, 1943, the patient contracted a cold in the head. Two weeks later he was hospitalized, with a temperature of 103 F, sore throat, a cough productive of bloody sputum and

general malaise. Unfortunately, roentgenograms were not taken during this hospitalization. After three or four days the patient was asymptomatic, and in one week he was returned to duty. The cough persisted, and pain in the lower left part of the chest developed. On April 6 he applied for Officers Candidate School. A roentgenogram taken at this time showed pneumonitis in the lower lobe of the left lung, for which he was again hospitalized. The diagnosis at this time was atypical pneumonia of the lower lobe of the left lung. Physical examination showed impaired breath sounds and rales in this area. The temperature was 101 F and the white blood cell count 7,100. Cough and purulent sputum steadily increased, and on April 21 bronchograms revealed bronchiectasis in the left lower lobe. The patient was then transferred to Percy Jones General Hospital. A second bronchogram, made on June 7, showed no improvement in the bronchiectasis, and clinically there was no alleviation of the symptoms. A lobectomy was performed on July 1. The pathologic examination of the removed lobe revealed complete consolidation of large areas as a result of extreme inflammation of bronchi and peribronchial

eral malaise occurred, for which he was hospitalized. Physical examination showed roughened breath sounds and rales at the base of both lungs but no evidence of dullness. The white blood cell count on January 18 was 11,200 and by January 25 had returned to 7,400. The sputum showed no significant organisms other than the usual bacterial flora. The first roentgenogram following the patient's admission to the hospital showed bilateral basilar bronchopneumonia (fig 8A). The fever subsided after four or five days except for an occasional afternoon elevation to 99 to 99.4 F. The cough became more productive over a period of the next several months. Rales and increased dullness at the base of the left lung posteriorly were constantly observed. The right-sided basilar pneumonitis showed roentgen evidence of clearance after three weeks, but the density at the base of the left lung fluctuated as to both severity and extent of involvement for the next three to four months, as shown in figure 8B. Plate-like areas of atelectasis were noted in the pulmonary field overlying the left part of the diaphragm that disappeared and recurred periodically during this time. Because of

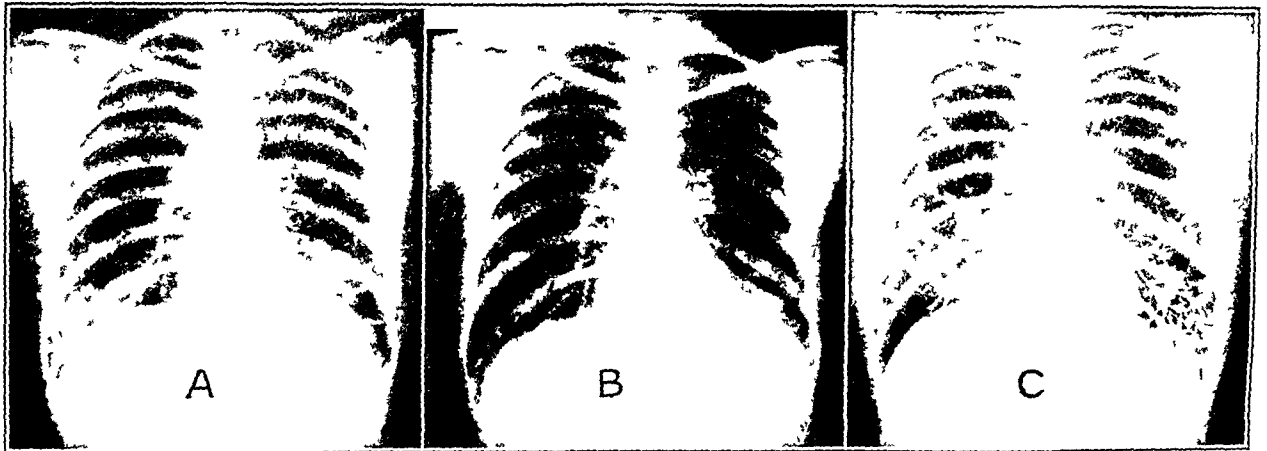


Fig 8 (case 6)—Development of bronchiectasis in a case of atypical pneumonia. A, original roentgenogram at the onset of atypical pneumonia, demonstrating bilateral basilar pneumonitis. B, roentgenogram taken three weeks later, demonstrating clearing of the pneumonia in the right lung but persistence at the base of the left lung for the next two months. C, bronchogram demonstrating the development of bronchiectasis at the previous site of unresolved pneumonia.

alveoli, together with pronounced atelectasis. The entire bronchial wall in places was destroyed and represented by merely a thick layer of inflammatory tissue composed largely of lymphocytes, plasma cells, histiocytes, polymorphonuclears and eosinophils. The bronchial epithelium was present but was abundantly infiltrated with polymorphonuclears and in many places had undergone desquamation. Within the inflamed mucosa and submucosa were innumerable newly formed dilated blood vessels. Only scattered strands of the muscularis were identified. The adjacent alveoli showed interstitial infiltration of similar type to that of the bronchi. Within the larger inflamed bronchi, the exudate was massive and filled them completely. The alveolar parenchyma between the bronchi exhibited considerable desquamation of alveolar epithelium, especially in atelectatic areas.

CASE 6—This patient was a 26 year old white man who during infancy had had measles but otherwise had enjoyed excellent health. The induction roentgenogram was normal. On Jan 10, 1943 he contracted a cold in the chest associated with cough and sputum. Five days later chills, temperature of 102 F and gen-

these observations, bronchographic examination was performed, which revealed extensive saccular bronchiectasis in the lower lobe of the left lung and the lingula (fig 8C). The patient was then transferred to Percy Jones General Hospital. After a period of approximately six weeks, bronchographic examination was repeated. No improvement in the degree or severity of the bronchiectasis was noted. The symptoms remained unabated. Consequently a lobectomy and lingulectomy were done on May 30. The significant pathologic conditions of the resected pulmonary tissue were as follows. The microscopic sections revealed rather pronounced interstitial inflammation and fibrosis involving the peribronchial tissues and associated with decided dilatation of the bronchi. In addition there was considerable atelectasis, which in places was complete. The bronchoarterial sheaths showed abundant fibrous thickening and moderate cellular infiltration of plasma cells, lymphocytes and occasional eosinophils. The peribronchial and periarterial inflammation extended down to the smallest bronchus. The basic lesion here appeared to be interstitial, being confined chiefly to the peribronchial regions. Moderately ex-

tensive saccular and cylindric bronchiectasis was present

CASE 7—This patient was a 25 year old white man. The past history was noncontributory except for measles, whooping cough and chickenpox as a child and pneumonia at the age of 16 without sequelae. The induction roentgenograms were normal. On Feb 8, 1943 he contracted a cold in the head and chest characterized by fever, cough, blood-tinged sputum, sore throat, nasal discharge and general malaise. Physical examination at that time revealed a nasopharyngitis, but the chest was normal. The temperature was 103 F and the white blood cell count 4800. On the following day on the basis of a roentgenogram of the chest a

weeks but recurred around April 1, 1943. The amount of sputum increased to the extent of 2 to 4 ounces (60 to 120 cc) daily. Because of the persistence of this productive cough bronchograms were made on September 9. Extensive bronchiectasis of the lower lobe and lingula of the left lung was demonstrated. The patient was then transferred to Percy Jones General Hospital. Bronchographic examination on October 10 and November 18 (fig 9) showed no alleviation of the bronchiectasis. Because of the previous empyema, lobectomy has been delayed.

Representative case histories are presented of 7 of the 17 patients seen at this hospital whose



Fig 9 (case 7) —Serial bronchograms over a period of three months demonstrating no change in the degree of bronchiectasis during this time in a patient who previously had had atypical pneumonia

diagnosis of atypical pneumonia of the base of the left lung was made. On February 10 rales were first heard in this area. The sputum showed only the normal bacterial flora. By March 2 a new pneumonic process appeared in the upper lobe of the right lung but there was clearing in this area after several weeks. Soon thereafter left-sided pleural effusion developed. This effusion remained sterile for approximately six weeks and then gradually became thickened. The white blood cell count at this time was 24,000. Culture now showed a hemolytic streptococcus. The empyema was drained on April 4. After drainage atelectasis of the left lung was noted, which persisted for several months. Complete healing of the empyema occurred by August. The initial productive cough subsided after several

bronchiectasis as far as can be determined, followed an attack of atypical pneumonia. Their attacks of atypical pneumonia were prolonged, and continuance of a productive cough and roentgen evidence of pulmonary pathologic conditions led to bronchographic examination and establishment of the diagnosis of bronchiectasis. Bronchographic examinations were repeated over a period of two to six months to rule out pseudo-bronchiectasis. Pathologic examination of the lobes resected proved the permanency and irreversibility of the condition.

In view of the large number of patients who have had atypical pneumonia without complications, the incidence of secondary bronchiectasis is undoubtedly small. It cannot be too strongly emphasized, however, that continued rest in bed should be insisted on until all evidences of pulmonary infection have disappeared as determined both roentgenologically and by physical examination. Van Ravenswaay stated that the sedimentation rate is a reliable index as to activity in such cases. When the atypical pneumonia runs a protracted course, and particularly when it is associated with roentgen evidence of unrelieved atelectasis, all measures should be taken to relieve

the bronchial obstruction and atelectasis. Such agents would consist of expectorants, steam and menthol inhalations and postural drainage. If these fail, bronchoscopic aspiration should be done, at which time the edematous ulcerated membrane could be shrunk with epinephrine hydrochloride. If the productive cough persists, bronchiectasis should be suspected and bronchograms should be made.

Twenty-one of the entire group of 45 patients with bronchiectasis have had lobectomies, with complete relief of symptoms. There was no operative mortality.

DETERMINATION OF SEDIMENTATION RATE OF RED BLOOD CELLS

USE OF SO-CALLED CORRECTION CHARTS AND OPTIMUM LENGTH AND DIAMETER OF THE PIPET

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"Correction charts" by which the observed values for the sedimentation rate are supposed to be corrected are used in many hospitals and by many practitioners in the United States. The scientific background of these correction charts is rather dubious. I began to check this scientific background after observing some instances in which in spite of a correct technic and a correct use of the correction chart the value calculated for the sedimentation rate was "negative." When I asked workers in laboratories in New York, Chicago and San Francisco about their experience in this respect, the reply was that several of them also remembered cases in which the value for the sedimentation rate was found to be "negative" after "correction" with a correction chart. Osgood¹ likewise observed such results. At my request Dr E. Moss put at my disposal the reports of the determinations of the sedimentation rate made in the laboratory of hematology of the Charity Hospital of Louisiana in New Orleans. These were made by skilful technicians. Determinations made in the small laboratories of the wards were not included. The results of 490 determinations of the sedimentation rate were reported. Of these, not less than 28 (5.7 per cent) showed a "negative" value after correction with Wintrobe and Landsberg's chart.

It is obvious that a method which gives such absurd results in 5.7 per cent of cases must be regarded as unreliable. It is instructive, however, to try to retrace the pseudoscientific background of these correction methods. The first correction chart was constructed in 1928 by Gram,² whose name is also connected with the well known staining method. The leading thought of Gram was that the reading of the sedimentation rate would be more correct if he excluded the influence of a reduction of the erythrocytes below normal. To construct the

chart, he altered the cell volume percentage of normal blood by addition of normal plasma in order to obtain samples with hematocrit readings between 26 and 40 volumes per cent. Two years later (1930) Rourke and Ernstene³ tried to improve Gram's correction chart by the same sort of procedure, but by adding only so much normal plasma to the normal red blood cells that the hematocrit reading became 45. Moreover, they used heparin as an anticoagulant and warned that their chart was constructed only for heparinized blood and not for blood mixed with other anticoagulants. Five years later (1935) Wintrobe and Landsberg⁴ attempted a third correction. Their chart had the advantage that it was constructed for readings of the sedimentation rate at the end of one hour. It did not require Rourke and Ernstene's time-consuming recording of degrees of settling at frequent intervals, which has, indeed, no practical value, in my opinion. Oxalated blood was diluted with increasing quantities of its own plasma. In this way six to nine dilutions were made of each sample of blood and 21 experiments were carried out, with the blood of 13 normal men and 8 normal women. The accuracy of this chart was tested with pathologic blood, obtained from 31 patients suffering from varying degrees of anemia. The sedimentation rate and the hematocrit-reading were determined. This was repeated after concentration of the blood by withdrawal of plasma. (Details may be found in the original article.) The results were compared with the readings obtained from the chart constructed as has been described. The conclusion was "It will be seen that the correlation, although not perfect, is nevertheless quite high." This conclusion sounds too optimistic if one checks the readings. Also this method of testing the accuracy of a chart is questionable. When Wintrobe and Landsberg's tables are checked, it appears that in the 45 com-

1 Osgood, E. E. *A Textbook of Laboratory Diagnosis*, ed. 3, Philadelphia, The Blakiston Company, 1940, p. 255.

2 Gram, H. C. *Acta med. Scandinav.* 68: 108, 1928.

3 Rourke, M., and Ernstene, A. *J. Clin. Investigation* 8: 545, 1930.

4 Wintrobe, M., and Landsberg, J. *Am. J. M. Sc.* 189: 102, 1935.

parisons of patients' blood with normal blood, not less than 11 subjects, that is, about 24 per cent, had a difference in the readings of the sedimentation rate of 9 mm or more (9 to 22 mm). With such differences one is not justified in calling the correlations "quite high." On the contrary, such results suggest that the correction charts are not reliable.

The unreliability of this method of testing the accuracy of a chart and the unreliability of the "correction chart" itself are probably due to the fact that the influence of the plasma proteins in normal and in pathologic blood is not sufficiently appreciated. The method would be reliable if only the hematocrit reading of pathologic blood were different from that of normal blood. However, increases of the percentage of globulin and of fibrinogen in pathologic blood are the main factors of an increased sedimentation rate. Disregard of these important factors is the reason that charts constructed on such a basis are doomed to give unreliable results.

From still another angle the construction of correction charts creates doubts. They are based on the premise that anemia causes an increase in the sedimentation rate. Therefore, they are constructed by figures obtained by dilution of the red cells of a normal blood by its own plasma. However, the premise that anemia increases the sedimentation rate does not hold good for all sorts of anemia, which proves that the fundamentals on which the whole construction is built are questionable. In New Orleans, where many persons with the sickle cell trait and with sickle cell anemia are observed among the Negro population, it is a well known fact that the sedimentation rate is low if a great percentage of the red cells are sickled. Winsor and Burch⁵ could confirm the findings of Bunting,⁶ who stated that sickled erythrocytes often remained almost un-sedimented after one hour. Winsor and Burch emphasized the influence of carbon dioxide on the shape of the red cell in sickle cell anemia and showed the diagnostic value of this influence. This, again, is probably an indirect influence of a chemical component of the plasma (HCO_3 , ion) on the sedimentation rate, in this case in a direction opposite to that of the influence of increased globulin and fibrinogen. It is another warning that it is not permissible to disregard the chemical composition of the plasma in pathologic conditions, which may be quite independent of the degree of anemia. Whereas sickle cell anemia may show a low sedimentation rate, pernicious anemia, if uncomplicated, sometimes may

show a normal sedimentation rate during the stage of anemia, although, as a rule, the rate is rapid. However, this possibility constitutes another argument against the fundamentals on which the correction charts are constructed.

That it is not so much the number of red cells per cubic millimeter as the radius of the red cell aggregates which determines the velocity of the sedimentation rate was pointed out by Fahraeus, the originator of the determination of the sedimentation rate. But this radius of the red cell aggregates depends on properties of the blood plasma. This can be demonstrated clearly by the following test. If erythrocytes from blood with a high sedimentation rate are suspended in plasma from a person with a low sedimentation rate, they settle at a lower rate. For this test one can use the erythrocytes of a pregnant woman and the plasma of a newborn infant.

Rourke and Ernstene tried to defend the construction of their correction chart with an appeal to the mathematician Cunningham.⁷ Stoke's law about falling objects was investigated by Cunningham⁷ in 1909. He stated that the velocity of a falling object decreases in the presence of other falling objects. However, in reading Cunningham's original article one finds no support for the construction of a correction chart. Only this may be concluded from Cunningham's investigations that the increased sedimentation rate of an aggregate of red cells would be still higher if one could exclude the influence of adjacent aggregates of red cells.

As far as the optimum length and diameter of the pipets are concerned, greatly varying conceptions are defended. A sad consequence of these controversies is that the results of several investigators cannot be compared accurately. I tried to find a solution for this problem by comparing the results obtained with pipets of varying lengths and tube diameters in combination with different kinds and varying dilutions of anticoagulants. The final decision was that longer pipets are preferable to the short ones now in vogue. This choice was made for three reasons. First, with a pathologically increasing sedimentation rate the plasma column is correspondingly much larger in the longer tubes, and thus pathologic results may be observed with more certainty. This is often of great value in dubious cases and especially in following the course of an individual case. Second, when the longer pipet, to be described here, is employed, it is possible to take advantage of the mass of statistics already compiled for the use of the

⁵ Winsor, T, and Burch, G. Personal communication to the author.

⁶ Bunting, H. *Am J M Sc* 198 191, 1939.

⁷ Cunningham, E. *Proc Roy Soc, London, s B* 83 357, 1909.

Westergren pipet, as will be demonstrated later. Third, in cases with a very high sedimentation rate it is often impossible to measure the rate when a short pipet is used. In such instances the opportunity for comparing results of successive determinations, often important in understanding the course of the disease, is completely lost.

To the advantage of sufficient length, I tried to add in the same pipet another advantage, a diameter which would permit the use of both venous and capillary blood. This is in contrast with Westergren's pipet, the diameter of which (2.5 mm) does not permit the use of capillary blood. The advantages of the possibility of using capillary blood for determination of the sedimentation rate are important and often insufficiently appreciated in the literature.

In a previous paper⁸ I pointed out the well known fact that in a small, but not negligible, number of patients venipuncture is not practicable. Osgood⁹ discussed this objection as follows: "This [objection] is valid and the older methods should be used on certain children and obese patients with small veins." However, in the case of the measurements of the sedimentation rate, suitable older methods of venipuncture do not exist. If venipuncture of the basilic or cephalic vein at the elbow of obese patients is impracticable, other veins, such as those at the ankle, are often also unfit for venipuncture. If the difficulty arises in children, blood may be obtained from the superior longitudinal sinus before the closing of the anterior fontanel or from the jugular vein. However, many physicians dislike taking the risk of puncture of veins in the neighborhood of the brain or of important cervical blood vessels and nerves. For these reasons determination of the sedimentation rate is not infrequently omitted in cases in which this procedure would have been of great value and could have been successfully carried out with a pipet suitable for the use of capillary blood. All the pipets commonly used at this time in the United States for the determination of the sedimentation rate are, according to their construction and directions for use, designed for venous blood. It seemed desirable, therefore, to try to perfect a pipet suitable for the use of both venous and capillary blood. The choice of the diameter of this new pipet was limited by several factors. A diameter of less than 1 mm could not be used because of the

effect of a too strong capillary attraction (Burger¹⁰). On the other hand, a diameter of more than 1.2 mm could not be used in a pipet adaptable for both capillary and venous blood because of the difficulty in retaining enough capillary blood to fill the tube. Moreover, it was important to choose a diameter with which, other things being equal, results would approximate those obtained with the Westergren pipet, the diameter of which is 2.5 mm. For this purpose readings of the sedimentation rate of 30 patients made with pipets having diameters of 1.2 and 2.5 mm respectively were compared.

Results Obtained with 2.5 Mm (Westergren) and with 1.2 Mm Pipet

Case	Pipet 2.5 Mm in Diam- eter	Pipet 1.2 Mm in Diam- eter	Case	Pipet 2.5 Mm in Diam- eter	Pipet 1.2 Mm in Diam- eter
1	7	8	16	14	14
2	5	5	17	13	13
3	5	5	18	5	5
4	4	4	19	6	6
5	20	23	20	8	9
6	9	10	21	3	2
7	8	7	22	4	5
8	20	17	23	3	3
9	16	13	24	14	15
10	9	11	25	11	11
11	5	5	26	9	9
12	10	11	27	2	2
13	2	2	28	20	21
14	16	16	29	2	2
15	5	5	30	20	20

The accompanying table shows that differences in results obtained with the two types of pipets are so small that the limits of normal as accepted for the Westergren pipet (2.5 mm in diameter) are undoubtedly also valid for the pipet of 1.2 mm diameter. Also for pathologic values the results are practically the same. As a result of these investigations a new pipet was made with a length of 30 cm and a diameter of 1.2 mm. It fits in the Westergren racks. It is also used for the preparation of a 4:1 dilution of the blood with a 3.8 per cent sodium citrate solution. It is filled either with venous blood by suction or with finger tip blood by capillary action. The plasma column is measured with a millimeter ruler. It has only four marks. More divisions were found to be superfluous.

It would facilitate the comparison of the values for the sedimentation rate obtained with different pipets if there were one generally accepted set of standard readings. Every one who wished to continue to use his favorite pipet could standardize his model with the standard readings. I spoke with many teachers and

⁸ Peters, J. T. Estimation of the Renal Function, with Aid of Iodosecretory Index and New Ureosecretory Index, *Arch. Int. Med.* **67**: 345 (Feb.) 1941.

⁹ Osgood,¹ p. 461.

¹⁰ Burger, H. *Arch. neerl. de physiol.* **15**: 565, 1930.

practitioners who complained seriously that at the present time accurate comparisons between results obtained with different pipets are not possible because of the varying "normal" values for different pipets. It is probable that the "Westergren normal" values will be chosen for this purpose, e g, by an international medical section of a postwar league of nations, because the Westergren pipet is by far the most commonly used throughout the world. With this pipet the largest number of values for the sedimentation rate has been collected for nearly every disease. Other pipets, each of which may have important advantages as well as disadvantages, have only local adherents. If all were standardized as just mentioned, it would be easy to decide which are the best ones. As far as the "Westergren normal values" are concerned, there is only discord among the investigators for certain age groups, namely for the age periods below $3\frac{1}{2}$ and above 65 years. It will be the task of a "standardization commission" to check these claims. For the time being, it seems advisable to admit two exceptions. The "Westergren normal values" may then be summed up as follows. The normal sedimentation rate, that is, the distance in millimeters which the red cell column falls in one hour, is 1 to 10 mm for men and 3 to 15 mm for

women. Excepted from this rule are values for subjects in the age groups between 1 month and $3\frac{1}{2}$ years and above 65 years, which may reach 20 mm.

CONCLUSIONS

The only safe and sound solution of the problem of "correction" of values for the sedimentation rate is to discard all correction charts and to evaluate the observed sedimentation rate by comparison with the clinical picture, since one knows from a large body of statistics how the sedimentation rate is usually affected in different diseases. Recording of degrees of sedimentation at frequent intervals is only time consuming and gives no more information than a reading at the end of one hour. Determinations of the sedimentation rate need no longer be omitted if venipuncture is not practicable, since a pipet can be made which is suitable for both venous and capillary blood. A long pipet is far preferable to a short one. Normal and pathologic values of the sedimentation rate are practically the same whether obtained with the Westergren pipet, which is 2.5 mm in diameter, or with a long pipet 1.2 mm in diameter, which permits the use of either venous or capillary blood. Thus one may profit from statistics compiled from millions of readings made with the Westergren pipet.

ADENOMA OF THE ISLETS OF LANGERHANS WITH HYPOGLYCEMIA

REPORT OF TWO CASES

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Hyperinsulinism is a broad general subject, touching on the fields of endocrinology, carbohydrate metabolism and neuropsychiatry. Furthermore, this condition presents itself in all degrees of intensity. Functional hyperinsulinism with mild hypoglycemic symptoms arising between meals or following mild exercise is common, but functioning tumors of the pancreatic islet tissue are uncommon, and even less common are growths which have been successfully removed at operation. These small adenomas of the islets of Langerhans produce recurrent severe hypoglycemic reactions, which at first yield to progressive increases of the intake of carbohydrates, but are finally cured only by the surgical removal of the adenoma. The present is a report of 2 cases of adenoma of the islets of Langerhans in which the tumors were removed surgically, with successful control after operation.

REPORT OF CASES

CASE 1 — History — The patient, a single white woman 24 years of age, was born and reared in North Carolina. She spent a normal childhood and had no severe illnesses. She did creditable school work, was graduated from high school and took one year of post-graduate secretarial work. It may be worthy of note that she never obtained "steady employment." Socially she was well adjusted, but she was regarded as something of a "tomboy" and repeatedly stated that she wished "she had been born a boy." There were no abnormal trends in her behavior on this score. The family history was noncontributory.

With this ordinary history, the patient had her first "attack" on June 15, 1940. On this day the girl slept later than usual and was roused with difficulty. On being awakened forcibly she seemed "drowsy" and "acted peculiarly." At the table she smiled foolishly and fell asleep over her breakfast. Next day the patient was well, and she behaved normally until the next similar attack. There were five such spells, each characterized by "sleepiness." The patient would retire and not awaken spontaneously in the morning. Shaking was always necessary. The longest period of "sleep" was twenty hours.

In the intervals between attacks the girl "cried easily" and "was not herself," but subjectively she complained of nothing until the most recent attack,

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when "double vision" bothered her. During this attack incontinence was noted. This was the only attack which occurred in the daytime. Several observers failed to note any convulsions, twitchings or abnormal motor phenomena, and "sleep" was said to be normal.

The local physician referred the girl to a university hospital for study. Examination on July 11, 1940 failed to reveal anything significant. The case was turned over to the department of psychiatry, and all efforts were directed toward discovering a cause of "narcolepsy." The examiner could reach no definite conclusion and discharged the patient after prescribing 10 mg of amphetamine sulfate twice a day. No improvement was noted.

Clinical Course — On September 11 the patient was referred to the Medical College of Virginia Hospital with the diagnosis of "brain tumor." At examination speech was thick and hesitant, the sensorium was clouded and there was disorientation in several spheres, but there was nothing to suggest a localized neurologic lesion. A psychiatric consultant did not establish a diagnosis.

The following day the patient lapsed into coma and could not be aroused by powerful stimuli. A lumbar puncture was done, and normal changes in pressure of the spinal fluid were found. The fluid contained 2 cells per cubic millimeter and 35 mg of protein per hundred cubic centimeters, the colloidal gold curve was normal. A determination of the sugar in the spinal fluid was not done. The concentration of bromides in the blood was 35 mg per hundred cubic centimeters, of nonprotein nitrogen 25 mg and of sugar 41 mg per hundred cubic centimeters. The blood count was normal in every respect. The Wassermann reaction was negative.

On September 13 the patient had a convulsive seizure, tonic in character, which involved all the extremities and lasted about a minute, during the seizure tongue biting and incontinence were noted. Stereoscopic roentgenograms of the skull showed a normal sella turcica, and there were no evidences of increased intracranial pressure or of displacement of any structure. Because of the low blood sugar content (41 mg per hundred cubic centimeters), feedings were given every two hours. Some improvement was noted, but there seemed to be no correlation between the symptoms and the intake of food.

On September 16 the fasting blood sugar level was 76 mg per hundred cubic centimeters, the total intake of carbohydrate being in excess of 300 Gm per twenty-four hours.

On September 17 the dextrose tolerance test (100 Gm of dextrose administered orally) gave the following readings during fasting, 70 mg per hundred cubic

centimeters, one hour, 200 mg, two hours, 135 mg, three hours, 91 mg, four hours, 74 mg, five hours, 52 mg

On September 23 the girl was crying and restless and refused her food. She was given 1,500 cc of 5 per cent dextrose solution intravenously. Her behavior became more normal after this infusion.

On September 24 ventriculograms were made, no abnormality was found.

On September 26 the fasting level of blood sugar was 36 mg per hundred cubic centimeters, in spite of the fact that at 9 o'clock the preceding night an infusion of 1,500 cc of 5 per cent dextrose solution had been given. An infusion of 2,000 cc of 10 per cent dextrose solution was given through the day, but the patient was not normal in her behavior.

On September 27 a maniacal outburst required that the girl be placed in a restraining sheet, and 6 grains (0.39 Gm) of sodium amytal was used for sedation. A stomach tube was employed, and 50 Gm of dextrose was given every two hours throughout the day and night.

On September 30 the history of the case was reviewed. The patient's mother stated that the girl had never complained of hunger or made special efforts to obtain food between meals. At this time the patient was receiving in the hospital 600 Gm of dextrose a day, and still the level of sugar in the blood was only 50 mg per hundred cubic centimeters two hours after a feeding of 50 Gm of dextrose. Surgical exploration of the pancreas was clearly indicated.

Surgical Procedure—On October 1 an infusion of 1,500 cc of 5 per cent dextrose in isotonic solution of sodium chloride was given immediately preoperatively, a similar infusion was given during the operation.

With the patient under general anesthesia, the abdomen was entered through a midline incision extending from the xiphoid to the umbilicus. An opening was then made in the mesocolon, and the pancreas was exposed. The body and the tail of the pancreas were carefully examined, but no abnormality was found. Palpation of the head of the pancreas revealed a small, firm nodule on the lower border of the head, in contact with the upper border of the third portion of the duodenum, this was regarded as a lymph node. The head of the pancreas was reflected by dividing the mesocolon on the right side and retracting the colon to the left. By this exposure of the posterior aspect of the head of the pancreas palpation was facilitated, and a small, firm nodule was felt within the pancreatic tissue. Several rather large vessels were found to supply this nodule, they were suitably ligated, and the nodule (a little over 1 cm in diameter) was excised. The bed of the nodule was closed with interrupted sutures of fine silk. The opening of the mesocolon was similarly closed. Palpation of the kidneys and of the adrenals revealed no pathologic conditions. The abdomen was closed without drainage. (This operation was performed by Dr I. A. Bigger.)

Pathologic Report—A microscopic section of the nodule revealed a central portion composed almost entirely of collagenous connective tissue, a few cells which appeared to be fibroblasts and in the periphery numerous rather large islets which seemed larger than normal and which were not situated within the usual acinar pancreatic epithelium. These islets had also an irregular arrangement, but the epithelial cells composing

them were regular and in no way differed from those found in a normal pancreas. In some of the islets, however, there was moderate collagenous connective tissue, which appeared to be similar to the tissue making up the greater part of the central portion of the nodule. Surrounding these structures was a small portion of what seemed to be normal pancreatic tissue. What few blood vessels and other structures were present appeared to be normal. There was no evidence of specific inflammatory change. The condition was diagnosed as benign adenoma of the islets of Langerhans of the pancreas with marked central fibrosis.

Course After Operation—Six hours after the operation the blood sugar was found to be 113 mg per hundred cubic centimeters, no dextrose had been given after the operation.

On October 3 the patient was mentally alert and more nearly normal than at any previous time during her stay in the hospital.

During the night of October 4 the patient fell out of bed, apparently because of a nightmare, there was no mental confusion.

On October 7 the patient was doing well clinically, but her bad humor and conduct were reminiscent of her preoperative behavior.

On October 13, the twelfth postoperative day, the girl left the hospital.

On the second, fourth, sixth and eight postoperative days the fasting levels of sugar in the blood were, respectively, 130, 92, 88 and 85 mg per hundred cubic centimeters.

Subsequent checks on this patient reveal that at the time of writing, two years after the operation, she is in excellent health.

Comment on Case 1—The total duration of symptoms was three and a half months, and until the last three weeks the chief complaint was the "sleepiness" on five occasions. Symptoms were so mild that the diagnosis of "neurosis" had been entertained. It is of interest that this patient had never complained of hunger and had never relied on ingestion of food to relieve her symptoms, indeed, the taking of more than 600 Gm of dextrose a day failed to control her symptoms while she was being observed in the hospital.

This case gives rise to certain interesting speculations. If the patient's first attack of "sleepiness" was due to overproduction of insulin by the adenoma—an assumption which seems justified, since her symptoms were promptly relieved by the removal of the adenoma—why were the symptoms not progressive from the time of their onset? An adenoma of a pancreatic islet is a new growth, and the cells which compose the adenoma are elaborating an active hormone, as is substantiated by the isolation of insulin or an insulin-like substance from the adenoma. Unfortunately we have no positive data as to the rate of growth of an adenoma, and we have no assurance that its size increases at a uniform rate. If the increase in size is constant it might be expected that the amount of insulin

produced would likewise progressively increase and that symptoms would be aggravated accordingly. In this case, however, while from the long range point of view symptoms were progressive in severity, the rate of evolution of symptoms in the last three weeks was out of proportion to that in the previous three months. Indeed, the isolated episodes of "sleepiness," with comparative freedom from symptoms between, speak for an inconstant, erratic overproduction of insulin. This observation would seem to harmonize with dysinsulinism, or disorderly production of insulin, as opposed to hyperinsulinism, or overproduction of insulin. We shall return to this point in the general discussion.

This case is witness to the truth that "hyperinsulinism takes another syndrome from the wastebasket of neuroses."¹ Hyperinsulinism should be considered, if only to be ruled out, as a possibility in every neuropsychiatric case.

CASE 2—History—The patient was a white woman, 67 years of age and widowed. She prided herself on her good health, had never suffered a serious illness and had passed through the climacteric at the age of 50 without incident. Five years before (1938) the complaint of "double vision" had taken her to a physician. A low level of blood sugar having been found on several occasions, she was advised to take 2 ounces (60 Gm) of dextrin every two hours. As a result of this program of increased intake of carbohydrate 30 pounds (14 Kg) was gained and the diplopia was relieved. In 1940 the patient began to have "attacks," which consisted in "failing to awaken in the morning" or in being overcome by sleepiness. This sleepiness was so insidious that the patient herself credited it only to her good fortune that she had been "found in time," for she was frequently unable to do anything to help herself. Nausea accompanying the attacks made the taking of food difficult when food was offered as a restorative.

Clinical Course—On Oct 19, 1942 this woman was admitted to the Medical College of Virginia Hospital. She was so obese that physical examination was of limited value. The patient was cooperative and was in no distress, she was slow of speech and had a coarse tremor of the hands and a slight weakness of the right side of the face. The optic fundi presented marked angiolar sclerosis and tortuosity, with prominent arteriovenous nicking, there were no exudates or hemorrhages. The blood pressure was 190 systolic and 130 diastolic in both arms, the heart sounds were poorly heard, the lungs were clear, no masses or enlarged viscera were felt in the abdomen.

On the afternoon of admission an attack was observed, the patient appeared dazed, looked vacantly into space, was unable to respond intelligibly, was disoriented and perspired profusely with a cold, beaded perspiration standing out on the forehead and the extremities, the weakness of the right side of the

face was more pronounced, the breathing was stertorous and the pulse full and bounding. There was no drop in the blood pressure. The patient had difficulty in swallowing, but shortly after being given 2 ounces (60 Gm) of dextrin orally she began to recover. She was able to talk clearly fifteen minutes later. There was complete amnesia with respect to the attack and for at least fifteen minutes prior to the appearance of the observable symptoms.

A diet including 300 Gm of carbohydrate and additional feedings of dextrin was prescribed, nevertheless there was an attack almost daily in the late afternoon or early evening, indeed, the attacks occurred so regularly that the nursing staff was able to recognize the patient's vacant stare and perspiring in advance of a "fully developed insulin shock" and to anticipate the attack by giving her dextrin or sweetened fluids. Determinations of the blood sugar at the onset of symptoms repeatedly revealed it to be low² 22, 40, 36 and 28 mg per hundred cubic centimeters.

Surgical Procedure—The patient's hypertension, cardiac enlargement, age and myocardial damage as demonstrated by electrocardiographic evidence made her a poor surgical risk, but the risk was accepted. An infusion of dextrose was given preoperatively and a second during the operation. With the patient under intercostal nerve block and intravenous pentothal sodium anesthesia, a right rectus muscle-splitting incision was made. There was a heavy layer of subcutaneous fat, and the underlying structures were extremely poor. The anterior rectus sheath, the rectus muscle and the posterior rectus sheath were exceptionally friable. There was heavy deposition of fat in the omentum and the abdominal structures.

The pancreas was exposed through an opening in the gastrocolic omentum. Almost immediately a firm nodule was felt at the tip of the uncinate process of the head of the pancreas. The body and the tail of the pancreas were palpated, and no other nodules were found. Exposure was difficult, and the nodule would have been more readily approached by reflection of the duodenum, but this was not feasible because of adhesions between the gallbladder and the duodenum, the cause of these adhesions could not be determined. The nodule was removed, but not without considerable hemorrhage from the rather large vessels supplying the nodule. The bed of the nodule was closed with interrupted mattress sutures. A frozen section of the nodule from the pancreas was returned by the pathologist with the notation that it was "compatible with pancreatic adenoma." A drain was placed in the lesser peritoneal cavity, but the drain was not in contact with the wound in the pancreas. The closure of the wound was unsatisfactory because of the poor quality of the tissues of the abdominal wall. The patient left the operating room in good condition. (The operation was done by Dr I. A. Bigger.)

Pathologic Report—The section consisted of a complete cross section of a well encapsulated nodule from the pancreas. On the external surface there was a small amount of recognizable pancreatic tissue containing both acinar tissue and a few islets. The nodule was composed of nests of uniform cells with vesicular nuclei and a moderate amount of cytoplasm and having a striking resemblance to islet cells of the pancreas. The nests of cells were separated by broad bands of hyalinized fibrous connective tissue, which made up probably

¹ Evans, J. A. and McDonough, W. Hyperinsulinism. Case Reports and Discussion, J. Iowa M. Soc. 23: 454-460, 1933.

one fourth of the area of the nodule. The diagnosis was a benign islet cell adenoma of the pancreas (nesidioblastoma).

Course After Operation—The blood sugar was 93 mg per hundred cubic centimeters nine hours after the operation, a value higher than any obtained preoperatively. Nausea and vomiting were troublesome for several days, and drainage from the wound was considerable, this having been anticipated because of the poor closure of the wound. There were no further attacks, the patient felt remarkably well, and was discharged to a convalescent home on Nov 23, 1942.

At the nursing home the patient did well for a few days, but since she then began to vomit five to ten times per day, it was thought wise to readmit her to the hospital. Examination revealed a 30 pound (14 Kg) loss in weight and a clean operative wound with a small sinus, from which drained a small quantity of watery discharge. There was no digestion of skin

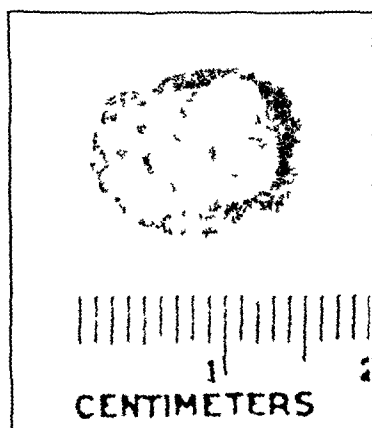


Fig 1—Tumor of the islets of Langerhans removed from the patient in case 2, showing fringe of pancreatic tissue around the well defined capsule. The tumor weighed 1032 Gm and measured 1 by 12 by 0.9 cm.

about the mouth of the sinus, and the blood pressure was 204 systolic and 140 diastolic.

A roentgen study of the gastrointestinal tract showed there was no deformity of the stomach or of the duodenum, but unusual looping of the second and third portions of the duodenum, with slight pressure on the greater curvature of the stomach compatible with enlargement of the head of the pancreas and pressure of the head of the pancreas on the pylorus and the duodenum.

The serum amylase was found to be 36 units (normal 20 units). On the basis of this finding and of the results of a roentgen examination it was suggested that the patient's nausea and vomiting were due to pancreatitis set up by the operation, so no active measures were taken by way of treatment.

Convalescence was uneventful, and the patient was discharged Dec 23, 1942.

The only laboratory work of significance in this case was that concerned with the metabolism of carbohydrates. This information is presented graphically (fig 4).

Comment on Case 2—This patient is one of the oldest patients on record who have recovered

after the removal of an adenoma of the islets of Langerhans. The recovery is all the more notable because of the factors which made her a poor risk.

The studies done on this patient were not numerous, and it may be unwise to postulate anything on the basis of so few data, but certain points brought out by the tests are of interest. The dextrose tolerance test was done after what is accepted as suitable preparation, i e, administration of 300 Gm of carbohydrate daily for three days prior to the test. The half-hour rise after the ingestion of 100 Gm of dextrose was distinctly of a diabetic type, and similarly the one, two and three hour levels of sugar in the blood may be called diabetic, yet the fasting level and the four hour level proclaim this curve to have been obtained from a patient with hypoglycemia. From this curve it may be inferred that there was marked intolerance for dextrose, but that insulogenesis was stimulated and that in four hours the fasting level was restored. It is of interest that the patient felt well at the termination of this test. This curve offers an interesting comparison with the one which resulted when the curve of tolerance for dextrose was modified by intravenous injection of 34 units of insulin. The second curve shows curtailment of the rise in the amount of sugar in the blood. From this curve it would appear that on practical grounds there is merit in Johns's recommendation that a small dose of insulin should precede feedings of a patient with hyperinsulinism in order to reduce the stimulus to insulogenesis. Since such a small amount of insulin modified the dextrose tolerance curve so markedly, the unmodified curve would seem to indicate that insignificant quantities of insulin were circulating in the blood at the time the dextrose tolerance test was begun and that only after stimulation by the ingested carbohydrate was enough insulin produced to lower the level of sugar in the blood to hypoglycemic levels. If this assumption is correct, it would seem that the adenoma of the pancreas is not constantly producing insulin in quantity and that the adenoma is, at least in some measure, controlled by the normal mechanisms which stimulate and inhibit the production of insulin. We shall return to this last surmise in the general discussion.

After the test for tolerance of dextrose and insulin combined, 0.7 cc of a 1:1,000 solution of epinephrine hydrochloride was given subcutaneously, and no rise in the level of sugar in the blood was obtained. Either epinephrine in this quantity was not capable of raising the level of sugar in the blood above the level already

existent, or this quantity of epinephrine could not offset the action of as little as 34 units of insulin given two hours previously. It might seem, then, that the observation in various cases of hyperinsulinism that epinephrine has an inconstant effect on the level of sugar in the blood may be explained by the different quantities of insulin acting at the times when epinephrine was administered.

The results of dextrose tolerance tests done postoperatively are presented in figure 3, together with the results of a preoperative test. The contrast is striking. There is little to be said concerning the curve done on Nov 20, 1942, but the curve of December 22 is unequivocally of dia-

GENERAL COMMENT

Despite the fact that the symptoms of hyperinsulinism are those of hypoglycemia, the terms are not synonymous. Conn² has offered a satisfactory classification of the various types of spontaneous hypoglycemia, and it is not the province of this paper to discuss hypoglycemia generally. We are specifically interested in the adenoma of the islets of Langerhans (insuloma³ or nesidioblastoma⁴) as a cause of hyperinsulinism and hypoglycemia.

Incidence of the Disease—Though there are fairly frequent reports of islet tumors, the removal of an adenoma at operation with re-

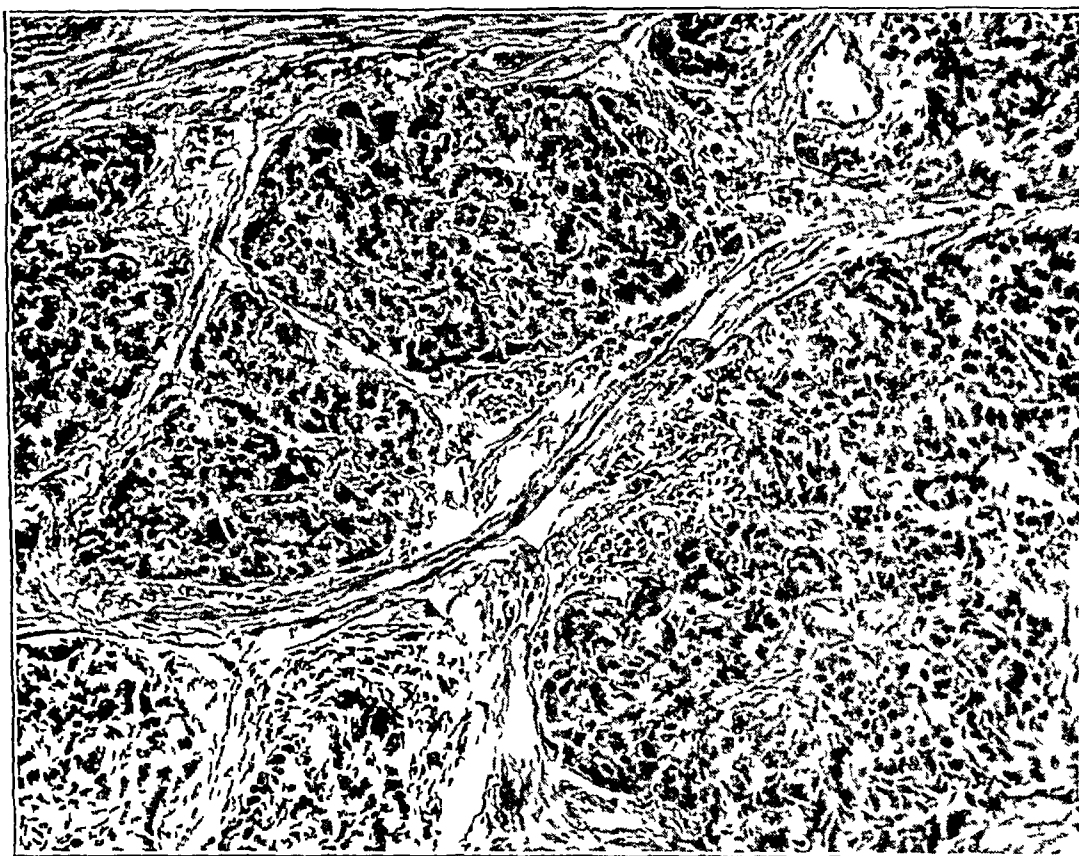


Fig 2—Photomicrograph of the tumor removed from the patient in case 2, showing bands of fibrous tissue. The pathologist's description appears in the text.

betic type. It would seem, then, that the patient was treated for an adenoma of the islet tissue, which produced hypoglycemia, and yet almost two months later she had a dextrose tolerance curve of definitely diabetic type. Transient diabetic tendencies during the first postoperative days are common, even ketonuria having been noted,² but such a definitely diabetic type of curve so long after operation has not been frequently reported. It is to be regretted that we lost contact with this patient and were unable to carry out further studies.

Recovery by the patient is still relatively rare. Frantz⁵ in 1940 reported 96 islet tumors with hypoglycemia, and Keating and Wilder⁶ in 1941 raised the number to 106, but analysis of these figures reveals that only 44 were benign pancreatic adenomas successfully operated on. We

3 Harris, S. The Diagnosis of Surgical Hyperinsulinism, *South Surgeon* 3:199-210, 1934.

4 Laidlaw, G. F. Nesidioblastoma, the Islet Tumor of the Pancreas, *Am J Path* 14:125-134, 1938.

5 Frantz, V. K. Tumors of Islet Cells with Hyperinsulinism. Benign, Malignant and Questionable, *Ann Surg* 112:161-176, 1940.

6 Keating, F. R., and Wilder, R. M. Spontaneous Hypoglycemia. Report of Cases, *South Med & Surg* 103:125-131, 1941.

2 Conn, J. E. The Spontaneous Hypoglycemia: Importance of Etiology in Determining Treatment, *J A M A* 115:1669-1675 (Nov 16) 1940.

have not reviewed the literature exhaustively, but we were able to find records of 10 more similar tumors.⁷ These cases together with those of Keating and Wilder are presented in the accompanying table. Thus with these 2 cases of our own the number of operative cures of pancreatic adenoma is raised to 56. This condition, therefore, is still rare.

Symptoms—The symptoms of these tumors are readily postulated as those of "insulin shock," but their multiplicity defies enumeration. Headache, weakness, dizziness, nausea, sweating, tachycardia, hypothermia, lowering of the blood pressure and diplopia are common. Neurologic signs and symptoms may be encountered alone or in any combination.⁸ The frequency of a positive Babinski sign, which disappears on the relief of hypoglycemia, is worthy of comment. Hunger has been emphasized in many reports, but both of our cases illustrate the fact that it is not a universal symptom. Convulsions are common and are by many considered characteristic of the condition, but patient 1 had convulsions only after three months of symptoms, and patient 2 in five years of symptoms was never observed to have a convulsion.

The lack of correlation between the occurrence of symptoms and the level of the sugar in the blood has been noted. The explanation for this lack of correlation is not clear. At one time the patient may have symptoms with a level of sugar in the blood which at another time produces no symptoms. Persons familiar with the use of protamine zinc insulin have noted the paradox

in the existence of symptoms of shock with blood sugar levels well over 100 mg per hundred cubic centimeters. It has been suggested that it is not the level of sugar in the blood per se which produces the symptoms, but the rapidity with which the hypoglycemia has been produced. If the fall in blood sugar is precipitous, symptoms will be elicited at a higher level than if the fall is gradual. The dextrose tolerance curve in case 2 is of interest in this regard. After the ingestion of 100 Gm of dextrose the decline to

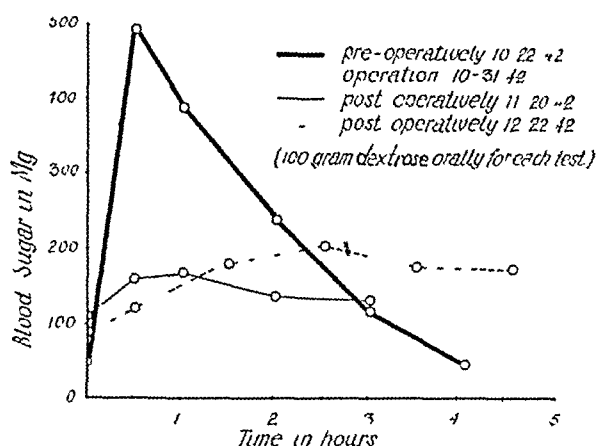


Fig 3—Results of the dextrose test for the patient in case 2, showing the effect on the blood sugar level of ingestion of 100 Gm of dextrose.

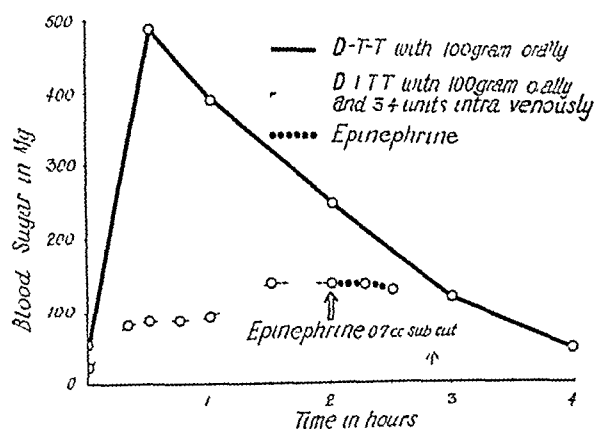


Fig 4—Carbohydrate study of the patient in case 2, showing modification of the dextrose tolerance curve by injection of insulin.

hypoglycemic levels was gradual, and the patient had no symptoms at the beginning of the test with a blood sugar level of 40 mg/100 at the end with a level of 48 mg/100. Hypoglycemia probably must be maintained a certain length of time before the central nervous system suffers sufficiently to cause a convulsion.⁹ Possibly the

7 (a) Meyer, K. A., Amtman, L., and Perlman, L. Islet Tumors of the Pancreas. Report of a Case, *J. A. M. A.* **117**:16-20 (July 5) 1941. (b) Vayo, P. G., and Bodon, G. R. Adenoma of Langerhans' Islet of the Pancreas, *Am. J. Surg.* **54**:744-746, 1941. (c) Magner, W. Hyperinsulinism. A Report of Two Cases, *Canad. M. A. J.* **45**:49-52, 1941. (d) Greenlee, D. P. Pancreatic Islet Tumors with Hypoglycemia, *Pennsylvania M. J.* **43**:809-812, 1940. (e) Burtess, H. I., Koehler, A. E., and Saint, J. H. Hyperinsulinism Due to Adenoma of the Islets of Langerhans. Case Report with Metabolic Studies Before and After Removal of Tumor, *Ann. Int. Med.* **14**:1915-1932, 1941. (f) Rudd, T. N., and Walton, J. A Case of Islet Adenoma, *Brit. J. Surg.* **29**:266-270, 1941. (g) Holman, E., Wood, D. A., and Stockton, A. B. Unusual Cases of Hyperinsulinism and Hypoglycemia, *Arch. Surg.* **47**:165-177 (Aug.) 1943. (h) Erb, W. H., Dillon, E. S., and Ferguson, L. K. Symposium of New Trends in Surgery. Islet Cell Adenoma, *S. Clin. North America* **22**:1663-1675, 1942. (i) Adenoma of Pancreatic Islet Cells, Cabot Case 27151, *New England J. Med.* **224**:659-660, 1941. (j) Conn.²

8 Sigwald, J. L'hypoglycémie, Paris, Gaston Doin, 1932. Wilder, J. Klinik und Therapie der Zuckermangelkrankheit, Vienna, Verlag für Medizin, Weidmann & Co., 1936.

9 Liu, S. H., Loucks, H. H., Chou, S. K., and Chen, K. C. Adenoma of Pancreatic Islet Cells with Hypoglycemia and Hyperinsulinism. Report of a Case with Studies on Blood Sugar and Metabolism Before and After Operative Removal of Tumor, *J. Clin. Investigation* **15**:249-260, 1936.

dextrose tolerance curve explains why patient 2 never had convulsions. Yet this suggestion is not wholly satisfactory, for cases are reported in which patients had blood sugar levels of 30 mg or less for a number of hours without any symptoms at all.¹⁰ The relationship between hypoglycemia and symptoms is still in need of clarification, especially since about 20 mg per hundred cubic centimeters of the blood sugar according to the Folin-Wu analysis is made up of reducible substance other than dextrose

subject to extensive fibrosis, hyaline degeneration and calcification.⁴ These observations have been made so frequently that no further comment is needed. Most adenomas are completely encapsulated, but even those tumors whose capsules are incomplete microscopically and show invasion by blood vessels behave like benign neoplasms. Frantz⁵ cited 15 cases of adenomas suspected of being malignant and removed at operation, some patients having survived five and ten years without recurrence of symptoms

Benign Adenomas of the Islets of Langerhans Removed at Operation with Recovery of the Patients

Reference (See Text)	Age	Sex	Duration of Symptoms	Type of Symptoms	Lowest Blood Sugar, Mg per 100 Cc	Tumor		Insulin Extracted	Comments
						Site	Size		
7a	41	F	18 mo	"Spells" "unconsciousness"	"Too low to read"	Body	2 by 1.8 by 1.5 cm	No	
7b	60	F	"Several mo."	"Stupor"	31 mg	Junction body and tail	4 by 4.5 by 2 cm	No	Associated Paget's disease
7c Case 1	52	M	8 yr	"Unconscious once daily for 5 yr"	35 mg	Junction head and body	2 cm in diameter	No	
6 Case 1	56	F	?	"Unconsciousness relieved by food"	38 mg	Tail	"Small"	No	Transient postoper- ative diabetes, retention cyst
Case 2 6	55	F	2½ yr	"Convulsions and unconsciousness"	38 mg	Head	?	No	Diabetes for 48 hr postoperatively
Case 3 6	33	M	18 mo	"Weakness, convul- sions, unconsciousness"	32 mg	Body	"Small"	No	Normal electro- encephalogram
Case 4 6	44	F	15 yr	"Unconscious spells for 4 yr"	40 mg	Body	"Small"	No	Pancreatic fistula
Case 1 7d	56	F	2½ yr	"Unconsciousness"	"Too low to read"	Junction tail and body	1.5 cm	Yes	Thyroiditis and hypoglycemia
Case 2 7d	61	F	6 mo	"Fainting, dizziness, convulsions"	29 mg	Tail	1 cm in diameter	Yes	
7e	43	F	7 yr	"Weakness, diplopia, personality change"	34 mg	Junction body and tail	1.5 cm (1.304 Gm)	No	Transitory diabetes mellitus
7f	29	M	8 mo	"Stupor, nervous- ness"	48 mg	Ligaments be- tween pancreas and spleen	1.3 cm	No	Extrapaneareatic location of adenoma
7g	?	F	6 mo	"Irritable, disori- ented, queer behavior"	37 mg	Tail and gastro- splenic ligament	0.7 cm and 2.0 cm	No	Extrapaneareatic adenoma, 2 tumors
7h	38	M	18 mo	"Sweating, clonic jerks of arm"	26 mg	Head	2 by 1 by 1 cm	No	Relieved for 6 weeks by diet and cortical hormone
7i	29	F	3 yr	"Always hungry, dizzy, coma"	26 mg	?	?	No	
2	59	F	10 yr	"Hunger, dazed spells, jerks of arm"	24 mg	Tail	From 0.5 to 1.5 cm	No	Four separate ade- nomas

But regardless of the clinical manifestations, which are so confusing that hyperinsulinism frequently masquerades as neurosis, brain tumor, epilepsy, narcolepsy and alcoholism, the diagnosis rests on the demonstration of a blood sugar value below 50 mg per hundred cubic centimeters and on symptoms which are relieved by the administration of carbohydrates. These conditions are readily met by a case of adenoma of the pancreatic islets.

Pathologic Changes—Pathologically, islet tumors are gigantic islets and produce lesions of the islets on a grand scale, for nontumoral islets are

Nevertheless frank carcinoma with metastases has been frequent enough¹¹ to compel us to regard these adenomas as neoplasms.

10 Murphy, R. G., Dustin, C. C., and Bowman, R. O. Hyperinsulinism Due to Adenoma of the Pancreas, *J. Lab. & Clin. Med.* **24**: 1050-1054, 1939.

11 (a) Holman, Wood and Stockton⁷⁸ (b) Wilder, R. M., Allan, F. N., Power, M. H., and Robertson, H. E. Carcinoma of the Islands of the Pancreas. Hyperinsulinism and Hypoglycemia, *J. A. M. A.* **89**: 348-355 (July 30) 1927. (c) Iudd, E. S., Faust, L. S., and Dixon, R. K. Carcinoma of the Islands of Langerhans with Metastases to the Liver Producing Hyperinsulinism. Report of a Case, *West J. Surg.* **42**: 555-557, 1934. (d) Cragg, R. W., Power, M. H., and Lindem, M. C. Carcinoma of the Islands of Langerhans with Hypoglycemia and Hyperinsulinism, *Arch. Int. Med.* **60**: 88-99 (July) 1937. (e) Joachim, H., and Banowitch, M. M. A Case of Carcinoma of the Islands of Langerhans with Hypoglycemia, *Ann. Int.*

(Footnote continued on next page)

Still, certain facts indicate that these tumors of the islets are unusual in their behavior

1 Why are the tumors so uniform in size, regardless of the length of time the patient has had symptoms? The average diameter is 0.5 to 1.5 cm, most of the tumors are described as "about a centimeter in diameter," and one more than 2 cm in diameter is unusual. Patient 1 had symptoms for three and one-half months and patient 2 for five years, yet the tumor in each instance was about 1 cm in diameter.

2 The component cells of these tumors secrete an active hormone.¹² If these cells are neoplastic one would expect them to secrete regardless of the need of the body for their secretion. Why, then, are symptoms not steadily progressive once they appear? In the description of both of our cases we have pointed out that between "attacks of sleepiness" there was relative freedom from symptoms. This would seem to indicate inconstant production of excessive insulin.^{7a}

3 Why are some of the tumors comparatively cellular, while others are markedly fibrotic and even calcified? The vascularity of these tumors, frequently reported, is a strong point against any argument of insufficiency of the supply of blood. The small size of the tumors makes it unlikely that they outgrow their blood

supply, with resultant degeneration and fibrosis. Again, fibrosis cannot be entirely a matter of aging of the tumors, for in case 1 there was considerable fibrosis and yet symptoms had been noted for only three and one-half months. But the question can be asked whether it is accurate to consider the age of a tumor identical with the duration of symptoms. Surely these tumors do not produce symptoms the moment they exceed the size of normal pancreatic islets. What, then, is the critical size of the tumors, at which they produce symptoms?

4 Why are the tumors so frequently multiple?¹³ Frantz⁵ in describing 96 cases of islet tumors cites 11 in which there was more than one tumor.

These questions are raised not because we have the answers but because when one tries to answer them it becomes clear that one can best harmonize the observations that have been made by regarding islet tumors as functioning units in the endocrine system. As such they are subject to the same inhibition and stimulation as normal islets, but to a lesser degree because they are neoplasms.

Connection with the Physiology of Insulin—

The physiology of insulin is too complex to be discussed here, but certain aspects of the subject will be of service to us. Fraser and others¹⁴ pointed out that the effect of insulin in lowering the level of sugar in the blood is opposed by the action of adrenal cortical hormones in promoting glycconeogenesis and by the glycotropic hormone of the pituitary gland. Normally these antagonists are nicely balanced, so that they compensate for each other. In a case of hyperinsulinism in which symptoms are clearcut and hypoglycemia is controlled with difficulty, it seems accurate to say that the system of checks and balances has become inoperative. But, as we have pointed out, this point is not reached at once, indeed the patient may do fairly well for years. It seems that there is an important place in our concept of hyperinsulinism for a "compensating-decompensating" phase preceding the final appearance of intractable hypoglycemia. The factor which determines the issue is that on one hand there are physiologic mechanisms, while on the other there is a neoplasm, the pancreatic adenoma. If the neo-

Med **11** 1754-1759, 1938 (f) Flinn, L. B., Beatty, G. A., Ginsberg, M., and Memsath, F. Carcinoma of the Islands of Langerhans with Hypoglycemia and Metastases to the Liver, J. A. M. A. **117** 283-285 (July 26) 1941 (g) Ballinger, J. Hypoglycemia from Metastasizing Insular Carcinoma of Aberrant Pancreatic Tissue in the Liver, Arch. Path. **32** 277-285 (Aug.) 1941 (h) Bickel, G., Mozer, J. J., and Junet, R. Diabète avec denutrition grave. Disparition de la glycosurie et atténuation progressive de l'hyperglycémie à la suite du développement d'un carcinome insulaire du pancréas avec métastases hépatiques massives, Bull. et mem. Soc. med. d'hôp. de Paris **51** 12-21, 1935.

12 (a) Greenlee^{7a} (b) Wilder, Allan, Power and Robertson^{11b} (c) Bickel, Mozer and Junet^{11h} (d) Akerberg, E. Hyperinsulinism and Surgery, Acta chir. Scand. **83** 104-122, 1939 (e) Campbell, W. R., Graham, R. R., and Robinson, W. L. Islet Cell Tumors of the Pancreas, Am. J. M. Sc. **198** 445-454, 1939 (f) Derick, C. L., Newton, F. C., Schulz, R. Z., Bowie, M. A., and Pokorny, N. A. Spontaneous Hyperinsulinism. Report of Case of Hyperinsulinism Cured by Surgical Intervention, New England J. Med. **208** 293-298, 1933 (g) Graham, E. A., and Womack, N. A., The Application of Surgery to the Hypoglycemic State Due to Islet Tumors of the Pancreas and Other Conditions, Surg., Gynec. & Obst. **56** 728-742, 1933 (h) Isaji, M. On Islet Cell Adenoma and Islet Cell Carcinoma of the Pancreas, Frankfurt Ztschr. f. Path. **53** 178-207, 1939 (i) Kerwin, A. J. Fatal Hyperinsulinism with Cerebral Lesions Due to Pancreatic Adenoma, Am. J. M. Sc. **203** 363-370, 1942.

13 Conn² Wilder, Allan, Power and Robertson^{11b} Joachim and Banowitz^{11c} Graham and Womack^{12g}

14 Fraser, R., Albright, F., and Smith, P. H. Carbohydrate Metabolism. The Value of the Glucose Tolerance Test, the Insulin Tolerance Test, and the Glucose Insulin Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism. J. Clin. Endocrinol. **1** 297-306, 1941.

plasma is truly carcinomatous, growth is rapid and hypoglycemia is fulminating, a few such cases have been encountered. By far the majority of the tumors, however, probably grow slowly, and by this circumstance the endocrine compensatory mechanisms are called into play, so that even if the islet adenoma continues its growth at a slow but steady pace, the body is capable of adjusting at different levels of production of insulin. We feel that such a concept harmonizes with the observed facts in cases of benign pancreatic islet tumor.

Duff¹⁵ stated that there is no authenticated example of spontaneous cure occurring as a result of generative changes in an islet cell adenoma. Such a cure would be difficult of proof, but theoretically there is a possibility of spontaneous recovery with the proper concomitance of fortuitous events. Young¹⁶ has demonstrated in dogs that with repeated injections of extracts of the anterior lobe of the pituitary gland he can produce permanent diabetes. Because of the lack of a potent preparation this method cannot be applied to human beings, unless there were available a preparation with selective action affecting only the overproduction of insulin there would be a distinct possibility of disturbing other members of the endocrine system. Allen¹⁷ nevertheless suggested this therapy with Young's extract in the event of severe "insulin intoxication." Fraser and others¹⁴ pointed out that nature furnishes an interesting experiment in that "a patient with acromegaly may be at the stage of 'compensating hyperinsulinism' or may end by having hypoinsulinism like a 'Young dog'." In short, this last statement seems to contain the crux of the matter. From the anterior lobe of the pituitary gland may come the stimulus which determines overproduction of insulin by pancreatic islet tissues, or underproduction of insulin through overstimulation and exhaustion of islet tissues. Thus diabetes mellitus and hyperinsulinism stand in close relationship to each other through the common factor insulin, the production of which is immediately a function of the islets of Langerhans but is influenced by other members of the endocrine system.

The case of Bickel and others^{11b} is of great interest, for the patient in this case received as

much as 100 units of insulin daily, and as much as 240 Gm of dextrose was excreted in the urine in a day. It was observed that the glycosuria disappeared in the course of four months, so that more dextrose was tolerated than formerly when 100 units of insulin was given daily. This patient died, and a carcinoma of the islets of Langerhans with hepatic metastases was found, insulin was isolated from the primary growth but not from the hepatic metastases.

Though such a conclusion is purely speculative, it would seem that this case indicates that perhaps there was a supreme effort made by the anterior lobe of the pituitary gland to stimulate the production of insulin in a definitely diabetic patient and that some tissues of the islets responded and gave rise to a growth, which in this case became malignant. In this case, contrary to the experience with Young dogs, the stimulated islet tissues did not become "exhausted," but overleaped the bounds of normalcy and became malignant. But following the reasoning used in the Young experiments with dogs, in an adenoma of the islets of Langerhans which is overproducing insulin the anterior lobe of the pituitary gland by compensatory overproduction of glycotropic hormone might conceivably inhibit all of the normal islets of the pancreas, producing true diabetes, which is masked by the presence of the adenoma. Surgical removal of the adenoma should result in a diabetic state. We cannot refrain from commenting that in case 2 there was a truly diabetic curve even two months after operation. The observation of transient diabetes after adenomas are removed is almost universal, it seems nearly certain that if these cases are followed up some patients will prove to have permanent diabetes.

This adventure into the field of endocrinology may contribute little of practical import at present, but it is fruitful in the matter of understanding the broader implications of hyperinsulinism and of looking forward to the therapeutic attack on this condition with endocrine products.

Treatment—At present the treatment of adenoma of the islets is surgical removal as soon as the diagnosis is reasonably established. Dietary management by increasing the intake of carbohydrate alone finally fails to control the symptoms and may actually aggravate the disease. Diets high in protein, high in fat and moderate in carbohydrate have had some success in the management of mild hyperinsulinism of the functional sort, but not much in the handling of cases involving islet tumors. The use of insulin before meals to prevent the sharp postprandial rise in blood sugar and so lessen the stimulus to the

15 Duff, G. L., and Murray, E. G. D. The Pathology of Islet Tumors of the Pancreas, *Am. J. M. Sc.* **203**: 363-370, 1942.

16 Young, F. G. The Anterior Pituitary Gland and Diabetes Mellitus, *New England J. Med.* **221**: 635-646, 1939.

17 Allen, F. M. Hyperinsulinism: Spontaneous and Artificial Hyperinsulinism, *J. Clin. Endocrinol.* **1**: 595-603, 1941.

production of insulin is theoretically sound (see dextrose-insulin tolerance curve), but practice has been disappointing. Subtotal pancreatic resection in the absence of a demonstrable tumor has been singularly unsuccessful in the treatment of hyperinsulinism.

Operation should be done early in these cases, for obesity is a natural development of the eating habits of these patients, and the technical difficulties of operation on obese patients are obvious. Long-standing hyperinsulinism can produce permanent damage to the central nervous system,¹⁸ and for this reason operation should not be too long delayed.

18 (a) Baker, A. B., and Lufkin, N. H. Cerebral Lesions in Hypoglycemia, *Arch Path* **23** 190-201 (Feb) 1937. (b) Baker, A. B. Cerebral Lesions in Hypoglycemia. II. Some Possibilities of Irrevocable Damage from Insulin Shock, *ibid* **26** 765-776 (Oct) 1938. (c) Klein, F., and Ligterink, J. A. Insulin and Cerebral Damage, *Arch Int Med* **65** 1085-1096 (June) 1940. (d) Kerwin ¹²¹

CONCLUSION

With the report of 2 of our own cases and 10 from the literature we have raised the number of benign adenomas of the islets of Langerhans which have been successfully removed at operation with recovery of the patients to 56.

A brief discussion of hyperinsulinism in its relationship to the endocrine system has been presented and the therapeutic implications stated. We believe that the study of this condition will be furthered if more attention is paid to the alterations produced in the other endocrine glands.

Surgical removal of these tumors is indicated as the most effective therapy, and this treatment is imperative in order to prevent damage to the central nervous system as a result of long-standing hypoglycemia.

The question of the cause of any new growth is challenging, but it seems doubly so in the case of a new growth which functions in the body's economy.

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LESIONS OF MUSCLE IN SPIROCHETAL JAUNDICE (WEIL'S DISEASE, SPIROCHETOSIS ICTEROHEMORRHAGICA)

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Few laboratories are equipped to perform the various procedures which may be needed for the diagnosis of spirochetal jaundice (Weil's disease, spirochetosis icterohemorrhagica). Larson,¹ in making a survey of leptospirosis among wild rats, concluded that multiple diagnostic methods should be employed since no single test always gave positive results in a sizable proportion of cases. Rather characteristic lesions in striated muscle in some cases of Weil's disease have been mentioned by Pick² and Jeghers, Houghton and Foley.³ This report deals with lesions encoun-

REPORT OF CASES

One patient (case 7) was a white man, while the others were Negroes. All had a history of exposure to rats. Two patients (cases 1 and 5) worked as poultry dressers. One patient (case 2) was a fish cutter, 1 (case 4) had been digging ditches just before his present illness while 1 (case 6) had cleaned out a fish pond. One patient (case 3) was a housewife, who stated that her home was infested with rats. One patient (case 7) worked at a dairy where rats were numerous. The age and the sex distribution are shown in table 1. Varying degrees of jaundice as well as enlargement of the liver were observed in every instance. The spleen

TABLE 1—Summary of Data on Seven Cases of Weil's Disease

Case	Age	Sex	Highest polymorpho nuclear Cells	Highest Nonprotein Nitrogen, Mg per 100 Cc	Highest Icteric Index	Agglutination L ictero haemorrhagiae	Day of Disease
1	33	M	23,000	61	92	1 10 1 1,000 1 100	10th 12th 33d
2	35	M	36,850	150	84	1 40 1 2,650 1 1,000	7th 17th 25th
3	46	F	38,500	35.4	141	1 3,000	13th*
4	40	M	21,600	57.2	105	Negative Negative 1 10,000	12th† 14th‡ 21st‡
5	37	M	19,300	41	55	1 10,000 1 10,000 1 100,000	8th‡ 15th‡
6	55	M	43,400	133	28.5	Negative	9th‡
7	29	M	16,450	41	27	Negative 1 1,000 1 1,000	8th 12th 18th

* Leptospiras were demonstrated by dark field examination from the liver of a guinea pig inoculated with the patient's blood.
† Done with commercial antigen only.
‡ Done by the National Institute of Health, negative results were obtained with commercial antigen.

tered in 16 biopsy specimens from muscles of the calf of 7 patients with Weil's disease seen recently at Grady Hospital.

From the Departments of Pathology of Grady Hospital and Emory University School of Medicine.

Read at the Second Annual Meeting of the American Federation for Clinical Research, held at Chicago on June 12, 1944.

1 Larson, C. L. Leptospirosis in Rats (*R. Norvegicus*) in and about Washington, D. C., Pub. Health Rep. 58 944-955, 1943.
2 Pick, L. Zur pathologischen Anatomie des infektiösen Icterus, Berl. klin. Wchnschr. 54 451 and 481, 1917.
3 Jeghers, H. J., Houghton, J. D., and Foley, J. A. Weil's Disease. Report of a Case with Post-mortem Observations and Review of Recent Literature, Arch. Path. 20 447-476 (Sept.) 1935.

was never enlarged. Muscular pains, particularly in the calves, were a constant feature in cases 1 through 6. This sign, however, was absent in case 7.

The principal laboratory data are shown in table 1. The clinical course was mild in cases 3, 4 and 5. In cases 1, 2 and 7 the patients were more seriously ill. Relapses, which are common with this disorder, were noted clinically in cases 1, 2, 4 and 7. One patient (case 6) died on the third day in the hospital.

The pertinent changes noted at autopsy in case 6 consisted of hepatitis, tubular nephritis, icterus, fibrinous pericarditis and petechial hemorrhages in the pleura, the gastric, intestinal and bronchial mucosa and the renal pelvis, consistent with Weil's disease. Attempts to demonstrate leptospiras by Levaditi's method were made on blocks from liver and kidney. Several suggestive structures were seen in the kidney, but it was felt that these were not unequivocal.

These 7 cases presented the clinical signs and symptoms of Weil's disease as discussed by Ashe, Pratt-

Thomas and Kumpe⁴ Agglutination tests gave positive results in all instances but case 6. It is of interest that agglutination tests gave negative results in cases 4 and 5 when done with commercial antigen (from Lederle Laboratories, Inc) but that the same specimens gave a strongly positive result when examined by the National Institute of Health, where live organisms are used.

The agglutination test which gave a negative result in case 6 was done only with commercial antigen and on the ninth day of the disease. This test generally

diagnostic. Only the demonstration of the organism in section is definite morphologic proof.

Dark field examination of blood and of urine gave negative results in all 7 cases. Guinea pig inoculation was done in cases 2, 3, 4 and 6. *Leptospiras* were demonstrated only in case 3, by dark field examination of the liver of 1 animal.

Material—Sixteen biopsy specimens were obtained in 7 cases. In all instances a small fragment of the gastrocnemius muscle, approximately 1 cm across, was removed under local anesthesia. Care was taken to

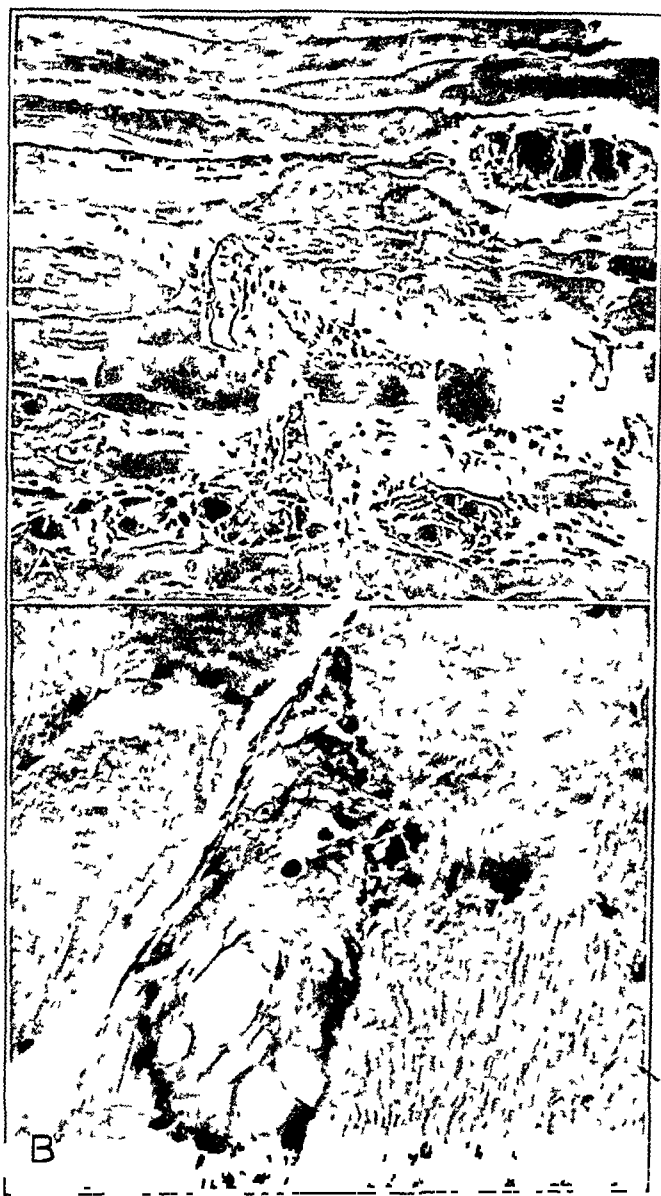


Fig 1—A, multiple focal areas of necrosis in striated muscle fibers. Most of the cells seen in the areas of necrosis are sarcoblasts, although the inflammatory cell infiltration in this case was unusually pronounced. Phloxine-methylene blue, $\times 120$. B, cytoplasmic vacuoles in a portion of one muscle fiber, with proliferation of sarcoblasts at both ends of the lesion. Outside the lesion the cross striations of the involved muscle fiber are preserved. Phloxine-methylene blue, $\times 290$.

gives positive results only after the ninth or tenth day of the disease. The observations at autopsy, both gross and histologic, were consistent with Weil's disease. At present, however, no single morphologic feature or combination of features can be regarded as absolutely

⁴ Ashe, W. F., Pratt-Thomas, H. R., and Kumpe, C. W. Weil's Disease. A Complete Review of American Literature and an Abstract of the World Literature, Seven Case Reports, *Medicine* 20:145-210, 1941.

infiltrate the tissues in such a fashion as to produce anesthesia in a fairly wide zone around the point from which the biopsy specimen was to be taken but to avoid infiltration of the tissue which was to be removed. In all instances the tissue was fixed within less than five minutes after removal. The tissue was fixed in both Zenker's fluid and solution of formaldehyde (10 per cent of the U. S. P. concentration), with the exception of 2 specimens, of which 1 was fixed only in Zenker's fluid and the other only in solution of formaldehyde. All Zenker-fixed material was stained with phloxine.

and methylthionine chloride (methylene blue), Mallory's phosphotungstic acid hematoxylin and Mallory's aniline blue. Turnbull's blue method for hemosiderin was used in some instances. Levaditi's method for the staining of spirochetes was employed on all material fixed with formaldehyde. Hematoxylin and eosin were used in the single case in which no Zenker-fixed tissue was available.

The lesions were shown clearly with routine fixatives and stains. Reasonable care should be taken not to traumatize the tissue during removal. It is advisable particularly in cases in which the condition is mild, to

When the specimens were studied in this order, the life history of the lesions could be followed readily. There were, of course, certain variations, according to the severity of the disease, in the individual cases. These variations, however, were quantitative rather than qualitative.

The lesions varied in number and extent. With mild forms of the disease, such as were found in cases 3, 4 and 5, relatively few small lesions were seen, while with more severe forms, as in cases 1, 2, 6 and 7, the lesions were numerous and larger. They always involved only a part of one muscle fiber. Sometimes



Fig 2—*A*, early necrosis in the cytoplasm of one muscle fiber. The transition between vacuolation and necrosis is visible. There is no significant inflammatory cell response. Phloxine-methylene blue, $\times 280$. *B*, sarcoblasts surrounding fragments of necrotic muscle. Inflammatory cells are few. Phloxine-methylene blue, $\times 460$.

cut six or eight sections. This will minimize the chance of missing the lesions if they are sparse.

No grossly visible changes were noted in any of the specimens.

Histologic Changes.—The 16 biopsy specimens were arranged in chronologic order, according to the day of the disease on which they were taken. The day of the disease was counted from the first appearance of symptoms noted by the patient. When arranged in this fashion the specimens ranged from the tenth to the sixty-sixth day of the disease (table 2).

Table 2 also shows the number of biopsy specimens taken from each patient.

TABLE 2—Day of Disease When Biopsy Specimen Was Taken

Case	Day
1	10, 17, 24, 31
2	17, 24, 35, 66
3	13, 36
4	13, 25
5	8*
6	13
7	11, 29

* The appearance of the lesion suggests that the disease may have been of longer standing than indicated by the history. The high agglutination titer (1:10,000) supports this impression.

two or even three adjoining fibers showed focal involvement. Rarely several independent foci were found in one single fiber. These sometimes became confluent, simulating a single large focus which involved a considerable portion of a muscle fiber (fig 1 *A*).

The earliest visible change consisted in the appearance of small and medium-sized vacuoles within a portion of the cytoplasm of the striated muscle fiber. These vacuoles tended to become confluent (fig 1 *B*). This stage is well illustrated by Jeghers and co-workers³ in figure 1 of their report. Simultaneously, the cytoplasm of the muscle fiber in the involved area lost its cellular detail. The longitudinal fibrils and the

a tiny recent hemorrhage into a muscle fiber was seen (fig 4). The first sign of cellular reaction consisted in the appearance of nuclei within the uninvolved portion of the fiber at both ends of the lesion. These nuclei were situated immediately beneath the sarcolemma sheath. They were rather large, oval and vesicular and had a prominent nucleolus (fig 1 *B*). Their number increased rapidly. Mitosis was seen often, but there were also indications of amitotic division. These elements extended along the sarcolemma sheath at the lateral margins of the lesion. Here they sometimes tended to assume a pearl-string-like or multinucleated syncytial arrangement. This was essen-



Fig 3—*A*, repair of the lesion by regeneration of striated muscle. The regenerated fiber stains darker, and the number of nuclei is increased. The nuclei still show a pearl-string-like arrangement. Note the absence of any fibrosis. Phloxine-methylene blue, $\times 500$. *B*, repair of the lesion with secondary fibrosis. The lighter-staining connective tissue displaces the sarcoblasts, some of which are multinucleated while others show segmented longitudinal fibrils. Phloxine-methylene blue, $\times 465$.

cross striations disappeared, and only fragmented masses of homogeneous or irregularly granular acidophilic material remained. The margins of the lesion were frayed and irregular but distinct (fig 2 *A*). The myofibrils and the sarcoplasm of the adjoining portions of the muscle fiber did not show any demonstrable changes. At this stage, no significant cellular reaction demarcated the lesion from the uninvolved portion of the fiber and generally no changes were noted in the interstitial connective tissue or in the adjoining capillaries, which, however, were congested. Only in 2 instances

totally the picture as seen on the tenth to the thirteenth day of the disease.

Meanwhile, these elements had become separate cells displaying the characteristics of sarcoblasts. They showed varying amounts of basophilic cytoplasm. Their shape ranged from round to elongated fusiform or often stellate with two or three processes. Coming from both ends, as well as from the margins of the lesion, they had invaded the area of necrotic muscle, which by now consisted of hyaline fragments. Some of the sarcoblasts had begun to encircle the individual

fragments of necrotic material, and in this process some large multinucleated cells had formed. Occasionally, some sarcoblasts appeared to have formed small niches at the margin of the fragment of necrotic muscle (fig 2B). This appearance suggested a digestion of the necrotic tissue. Polymorphonuclear leukocytes were seen infiltrating the necrotic area, but on the whole the inflammatory cell infiltration was not striking. No significant changes were noted in the adjoining interstitial connective tissue and capillaries. This was essentially the picture seen in the tissue removed on the seventeenth day of the disease.

At this stage, only slight new formation of myofibrils could be discerned. This consisted in the appearance of granules within the cytoplasm of the proliferating sarcoblasts, as seen with the phosphotungstic acid hematoxylin stain. These granules were arranged in a definite pattern longitudinal to the long axis of the cells. Longitudinal fibrils segmented at regular intervals by dark granules appeared, and cross striations became visible in the manner described by Wolbach.⁵

cells appeared in the interstitial connective tissue adjacent to the involved muscle. This was associated with some proliferation of fibroblasts, which grew into the area of necrosis and participated in the repair of the lesion. On the whole, however, the degree of inflammatory cell infiltration was slight and never formed a prominent feature of the lesion. The capillaries adjoining the lesion, as well as the larger vessels elsewhere throughout the section, did not display any demonstrable changes. This was the appearance of the lesion on the twenty-fourth day of the disease.

The latter stages of the process, as seen in the biopsy specimens obtained on the thirty-fifth and sixty-sixth day of the disease, showed the progress of repair by fibrosis. The fibroblasts had become more prominent and had begun to deposit collagen. The latter increased and appeared to encroach on the sarcoblasts, which showed signs of atrophy (fig 3B). In addition, but apparently not related to the scarring, small amounts of light brown refractile pigment deposited in granules had become visible in some of the sarcoblasts encircling the remaining fragments of necrotic muscle. This pig-

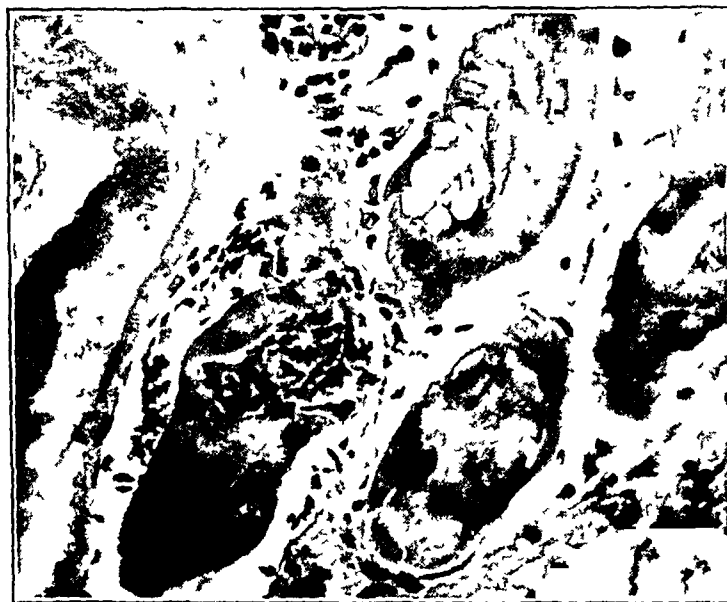


Fig 4—Early lesion with hemorrhage into one muscle fiber (left lower corner) and vacuoles in another (right upper corner). Other muscle fibers (lower center and right upper corner) show advanced repair. The recent lesions coincided with a clinical relapse lasting from the twenty-fourth to the twenty-ninth day of the disease in case 2. Phloxine-methylene blue, $\times 275$.

This repair became rapidly more active. In the cases in which the foci of necrosis had been few and small and the clinical course had been rather mild, the repair had been almost completed in a period ranging from the twenty-fifth to the thirty-sixth day of the disease. A few muscle fibers were seen which often appeared thinner than normal. Their cytoplasm stained rather dark basophilic. The nuclei beneath the sarcolemma sheath were more numerous than in normal muscle fibers and displayed some persistence of the pearl-string-like arrangement (fig 3A). No changes were noted in the adjacent interstitial connective tissue and capillaries.

Thus the lesion had been repaired by regeneration of the striated muscle without significant participation of the adjacent interstitial connective tissue. Therefore, no appreciable fibrosis and scarring had occurred.

When, however, the disorder was clinically more severe and complicated by one or several relapses, an inflammatory cell infiltration of lymphocytes and plasma

ment stained blue with Turnbull's blue method for hemosiderin.

Thus in the more severe lesions repair was accomplished by fibrosis.

In every case a large number of sections stained with Levaditi's method for spirochetes was searched for the organism. In only 2 instances structures suggestive of leptospiras were seen. It was felt, however, that these were not unequivocal.

COMMENT

The morphologic features of the lesions in the muscle correlated well with the clinical course. Early but definite lesions were present on the tenth day of the disease in case 1. Clinical relapses, which are common with this disorder, were marked by the appearance of new lesions besides the already existing older ones (fig 4). These new lesions followed the same sequence of events as described. This is well shown in case 1, in which the patient had a relapse with a rise

⁵ Wolbach, S. B. Centrioles and the Histogenesis of the Myofibrils in Tumors of Striated Muscle Origin, *Anat Rec* **37** 255-262, 1928.

of temperature to 102 F on the twenty-third and twenty-fourth day of the disease. The biopsy specimen taken on the twenty-fourth day of the disease showed early lesions of the type seen on the thirteenth day of disease in the other patients besides the older lesions which already displayed advanced repair. The taking of a biopsy specimen on the twenty-fourth day in case 2 coincided with a rise in temperature to 104 F from the twenty-fourth to the twenty-ninth day. This specimen showed a few recent lesions of the earliest type besides older ones. A similar picture was seen in a specimen taken in case 4 on the twenty-fifth day, when the patient's temperature rose from normal to 100 F.

Morphologically the lesion in the muscle appeared to be rather typical. The small focal distribution of the lesion and the absence of significant hemorrhage differentiated it from Zenker's degeneration. This had already been pointed out by Jeghers and his co-workers,³ who stressed the characteristic appearance of this lesion as compared with other lesions of muscle. The absence of vascular changes distinguished this lesion from those found in the muscles in cases of rickettsial infections. Control sections of gastrocnemius muscle were taken at autopsy in 2 cases of subacute yellow atrophy of the liver after arsphenamine treatment, in 1 case of non-obstructive biliary cirrhosis of the liver, in 2 cases of pneumococcal pneumonia with septicemia, in 1 case of staphylococcal septicemia and in 1 case of subacute bacterial endocarditis of the mitral and aortic valves. No lesions resembling those of Weil's disease were observed.

It is an acknowledged fact that Weil's disease can be diagnosed only by laboratory tests. These consist of dark field examination of the blood, urine or duodenal washings for demonstration of the organism, agglutination reaction, animal inoculation or culture. The findings in these 7

cases and those described in the literature suggest that the lesions in the muscles of the calf might be a constant and reliable feature of this disease. Since a biopsy specimen of the muscles of the calf can be taken without undue difficulty, this procedure is suggested as a possible aid in the diagnosis of Weil's disease.⁶

SUMMARY AND CONCLUSIONS

Lesions in the muscles of the calf were encountered in 16 biopsy specimens in 7 cases of spirochetal jaundice (Weil's disease, spirochetosis icterohemorrhagica).

The morphologic characteristics of these lesions are considered rather typical of this disease. The observations reported suggest that these lesions may be a constant feature of this disorder.

Biopsy of the muscles of the calf is suggested as a useful measure in the diagnosis of Weil's disease.

6 After this report was submitted for publication biopsy specimens of muscles were obtained from 12 other patients with suspected Weil's disease.

In 5 cases lesions of Weil's disease were found, but in only 1 did the patient show a positive reaction to an agglutination test. In another the reaction to an agglutination test was negative with commercial antigen, while the single blood sample examined by the National Institute of Health showed a positive reaction for *L. icterohaemorrhagiae* with a titer of only 1:100. The agglutination test in the other 3 cases always gave negative results.

In 1 of the remaining 7 cases Weil's disease was proved by an agglutination test. A single biopsy specimen of muscle was reported as showing nothing significant, but the tissue was too severely traumatized during its removal to permit adequate histologic study. A biopsy specimen from a patient with proved typhus was first considered indicative of Weil's disease, but further sections clearly revealed the typical vascular lesions of rickettsial infection.

Infectious hepatitis (3 cases), reaction to arsphenamine therapy (1 case) and atypical pneumonia (1 case) were found in the remaining 5 cases in which biopsy specimens gave negative results.

Progress in Internal Medicine

VASCULAR DISEASES

TENTH ANNUAL REVIEW

THEODORE R VAN DELLEN, M D , GEORGE W SCUPHAM, M D ,
GEZA DE TAKATS, M D, AND EDSON FAIRBROTHER FOWLER, M D
CHICAGO

REVIEW OF SOME OF THE RECENT LITERATURE

BY DR VAN DELLEN AND DR SCUPHAM

During the past year there has been a definite decline in the number of publications on peripheral vascular disease. Many noted and consistent workers in this field are obviously devoting their time and talent to the war effort. Some of these men have already collected and published valuable data obtainable only under wartime conditions. Publications associated with the physiology of vascular disease are not as numerous as in previous years, and statistical data on large series of cases are conspicuously absent. Attention should be called to the anti-coagulants, to fluorescein and to recent observations on periarteritis nodosa. Therapy has been totally neglected. As in the past, this review should not be considered complete, since many deserving articles have possibly been missed.

PHYSIOLOGY

Diagnostic Tests—Naide¹ recently reported a test for estimating vascular tone. This was determined by measuring the rate of fall in temperature of the extremities during a cold period and the rate of rise during a period of application of moderate heat to the trunk. Studies were performed in a constant temperature room at 20 C. Surface temperatures of the fingers and toes were recorded. The importance of readings of finger temperature lies in the fact that normally there is less tone in the vessels of the fingers than in those of the toes, and by observing the response to cold and to heat at these sites a gradient of vascular tone or ratio of vascular response in the feet to that in the hands can be determined. Moderate heat was used to prevent most normal persons from having vasodilatation, thereby distinguishing those who

were slightly vasospastic. Information of this nature was obtained for 53 normal persons, and a simple table was arranged in which these subjects were classified on the basis of vascular tone. Seven groups were obtained, ranging from persons with low to persons with high vascular tone. Patients with vascular disease were found to fall in the groups with vascular tone approaching high values. Sixteen of 17 patients with thrombophlebitis were also in the vasospastic groups. Nine of 32 patients with thrombo-angitis obliterans were in the group with low vascular tone. Various other studies were done in association with this test. The author was able to distinguish whether vasodilatation or vasoconstriction in different persons was located in large or small arteries by comparing the oscillometric index with the surface temperature. This test opened up a new approach to vascular study and was worthy of consideration for all interested in this problem.

Rinzler, Travell and Civin² correlated Atlas' oscillometric index with other objective evidences of vascular disease, namely, surface temperature and changes shown by roentgen examination of the vessels of the lower extremity. This index was described in a previous review. Studies were performed on 84 ambulatory patients. A correlation of the data obtained by these three laboratory aids (oscillometry, determination of surface temperature and roentgenography) showed that as the oscillometric index decreases, the incidence and extent of calcification of the lower extremity and the incidence of abnormal cutaneous temperatures increase. In contrast to the work of Atlas, these authors concluded that the index can be lowered from 1.0 to 0.75, as in their studies readings above the latter figure always indicated adequate arterial function in the lower extremity. An index below 0.75 in their opinion is pathologic and compatible with sclerotic changes, and a value below 0.3 indicates extensive calcification and probable ad-

From the Department of Medicine, Northwestern University Medical School, the Department of Surgery, the University of Illinois College of Medicine, and the Circulatory Group, St. Luke's Hospital.

1. Naide, M. A Test for Vascular Tone in Humans and Its Application to the Study of Vascular Diseases with Special Reference to the Etiology and Prevention of Thrombophlebitis, *Am J M Sc* 207:606 (May) 1944.

2. Rinzler, S. H., Travell, J., and Civin, H. The Oscillometric Index: An Aid in Evaluating the Arterial Status of the Lower Extremities, *Arch Int Med* 73:241 (March) 1944.

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vanced occlusive arterial disease. The authors discussed oscillometric readings in general and concluded that a reading of more than 4 at the ankle or more than 2 at the foot nearly always indicates normal arterial flow. A reading of less than 1 at the ankle or 0 at the foot is in their opinion indicative of occlusive arterial disease.

Foregger³ studied the effect of the commoner anesthetic agents on the surface temperature of normal persons. A maximum increase with full vasodilatation of the peripheral vessels was produced by inhalation of nitrous oxide, ethylene, cyclopropane, ether and chloroform. This phenomenon occurred in the first phase of anesthesia if maintained for several minutes. As a rule there was no fall in arterial pressure. Maximum dilatation also followed spinal or local block anesthesia. Lumbar sympathetic block was not found to be entirely satisfactory, as it was painful and uncertain. Intravenous injection of pentothal sodium produced a good response, and only a light plane of anesthesia was required. The author presented excellent charts, which can be considered as records of normal responses to the drugs administered.

Two preparations have recently been introduced for visualizing the arterial tree in post-mortem specimens. These are of value not only because they are radiopaque but because they facilitate dissection. Tobin⁴ used a pigmented liquid latex solution combined with a mixture of ethyl esters of iodophenylundecylic acid (pantopaque). Epstein⁵ employed a mixture of lead tetroxide (red lead) and glue. He found this most useful in studying the blood supply to lymph glands and nerve tissue.

Circulation Time—The intravenous administration of fluorescein for measuring the circulation time was reported in last year's review. Additional articles have been noted which elaborated on its usefulness or described improvement in technic. Lange and Boyd⁶ measured the arm to face circulation time in 212 normal adults. The time ranged between fifteen and twenty seconds, the majority of values being between fifteen and seventeen and five-tenths seconds. The appearance of fluorescein in the hip under a special source of long wave ultra-

violet radiation was used as the end result. These readings are in keeping with those obtained by most methods but slower than those obtained by others. The observations are consistent with results of previous investigations of the circulation times in the aged, during fever or work, and in the presence of failure of the right side of the heart, asthma, hyperthyroidism, hypothyroidism and anemia. They also demonstrated that fluorescein can be used to determine the velocity of the flow of blood to different parts of the body. The average time of circulation to the conjunctiva, lips, rectum and foot was ten, fifteen, eighteen and twenty-three seconds, respectively. The time to the conjunctiva was the shortest, but for obvious reasons this area was not recommended. The authors also compared their results with those obtained with acetylene inhalations, using the latter to measure the time which elapsed until all blood in rapid circulation had passed the lungs at least once. This was labeled as the "slowest circulation time."

Sicher⁷ reported on his experience with fluorescein. Since his light was small, only a part of the body was illuminated at one time. Readings were routinely taken from the lips, fingers, base of the toes and other structures, depending on the pathologic condition being studied. The circulation time was prolonged in cases of peripheral vascular disease, and in certain cases fluorescein was not detected in an ischemic toe after ten minutes' observation. The author stressed the fact that fluorescence does not occur until blood bearing the dye has made its way well up into the arterioles and capillaries of the skin. It is essentially a surface phenomenon and directly influenced by possible variations in arteriolar and capillary tonicity, in dilatation or constriction. The observations indicate that the results of the test coincide well with the physical findings of peripheral arterial obstruction. The article is followed by a few statements concerning the physical and biophysical nature of the phenomenon of fluorescence.

In a more recent article, Lange and Kiewer⁸ described an instrument for the objective measurement of the fluorescence of the skin and organs and the determination of circulation time and capillary permeability. This instrument is

3 Foregger, R. Surface Temperatures During Anesthesia, *Anesthesiology* 4: 392 (July) 1943.

4 Tobin, C. E. A Radiopaque Liquid Latex Injection Medium for Blood Vessels, *Am J Roentgenol* 51: 386 (March) 1944.

5 Epstein, J. A Method for Visualizing the Blood Vessels of Nerves and Other Tissues, *Anat Rec* 89: 65 (May) 1944.

6 Lange, K., and Boyd, L. J. Objective Methods to Determine the Speed of Blood Flow and Their Results (Fluorescein and Acetylene), *Am J M Sc* 206: 438 (Oct) 1943.

7 Sicher, W. D. Circulation Time of the Extremities Using Intravenous Administration of Fluorescein, *Proc Staff Meet, Mayo Clin* 18: 515 (Dec 29) 1943.

8 Lange, K., and Kiewer, S. E. Dermofluorometer Instrument for Objective Measurement of Fluorescence of Skin and Organs and Objective Determination of Circulation Time and Capillary Permeability, *J Lab & Clin Med* 28: 1746 (Nov) 1943.

called the deimofluorimeter. It consists of two parts. The first is a small light emitting blue rays which are directed toward the skin at an angle. The reflection of this light is registered on the second part, which contains a phototube. This reflected light is yellow-green, depending on the fluorescence of the blood stream. Filters allow only the proper light to come into contact with the phototube. This instrument deflects light in direct proportion to the concentration of fluorescein present. Objective measurements are thus possible for determining both circulation time and capillary permeability.

Effect of Drugs—Stead and Warren⁹ injected histamine into the brachial artery in human beings and noted that it increased the permeability of capillaries supplied by this artery. A rapid loss of protein from the plasma was detected by comparing the blood draining from the part before and after the injection. The hematocrit reading and the hemoglobin concentration increased greatly, while the protein concentration rose only slightly. The authors failed to notice a similar action in uninjured tissue in the usual types of shock.

The variations in blood flow to the fingers following the intramuscular injection of nicotinic acid, priscol (2-benzyliminazoline), eupaveine (methylenedioxybenzylmethylenedioxyquinoline) and prostigmine methylsulfate were discussed by Introzzi and his colleagues.¹⁰ Studies were performed on 17 normal persons and 4 patients with Raynaud's syndrome. The blood flow was measured with the plethysmograph. The results were inconstant, especially for normal subjects. The temperature of the skin rose considerably with eupaveine and priscol, and the central temperature generally decreased with nicotinic acid. For 2 of the patients with Raynaud's syndrome prostigmine was found effective, but the authors considered the series too small to be of significance.

Redisch and Pelzer¹¹ studied the peripheral capillaries of patients with migraine before and after the intravenous administration of 0.25 to 0.5 mg of ergotamine tartrate. Studies were made with the capillary microscope. Impaired visibility of the surface outlines of the capillaries was observed during 142 attacks of migraine in

118 patients. After the administration of ergotamine tartrate to 23 of these patients changes were noted in 20. This led the authors to believe that a disturbance in water balance might exist during the attack of migraine, and experiments were performed after the administration of 1,500 cc of water. Fourteen of the 15 patients thus studied were found to have an abnormal "excess secretion" of urine. As this excess secretion subsided, a migraine headache developed in 21 of the 29 experiments. Headaches did not develop in 4 of the patients who had a normal response to the ingestion of water. When ergotamine tartrate was injected during the height of the water-induced headaches, relief was obtained, but usually associated with diuresis and profuse perspiration. These results are difficult to explain, but the authors believe that a relationship exists between fluid balance, the state of the peripheral capillaries and migraine attacks.

Levinson and Essex¹² made direct observations on the reaction of the small blood vessels in the rabbit's ear to epinephrine, ephedrine, ergotoxin and pitressin before and after denervation. Studies were made after stimulation of the auricular nerves and cervical sympathetic chain. An attempt was also made to correlate the reactions of the blood vessels with necropsy evidence of regeneration, in an effort to determine the function of the nerves innervating these vessels. The vessels were observed through a Clark transparent chamber, which has proved suitable for this type of study. Epinephrine caused a constriction of the arterioles accompanied by a slight narrowing of the venules. Ephedrine produced a similar response, but there was evidence of a refractoriness to repeated doses. Pitressin in the dosage used (0.1 pressor unit per kilogram of body weight) resulted in the most pronounced vasoconstriction, but refractoriness to repeated injections was also noted. Ergotoxin blocked the vasoconstrictor action of epinephrine. Stimulation of the cervical sympathetic chain produced a constriction of the arterioles in the window more consistently than did stimulation of the dorsal or great auricular nerves. The denervated vessels became hypersensitive to epinephrine and seemed to regain their tone after this procedure. The blocking action of ergotoxin was also altered by denervation.

Tobacco—There is sufficient evidence to date to substantiate the fact that smoking will de-

9 Stead, E. A., Jr., and Warren, J. V. The Effect of the Injection of Histamine into the Brachial Artery on the Permeability of the Capillaries of the Forearm and Hand, *J. Clin. Investigation* **23**: 279 (March) 1944.

10 Introzzi, A. S., Cabanne, E. A., and de Soldati, L. Plethysmographic Studies on the Action of Various Drugs on Caudal Flow of Blood, *Rev. argent. de cardiol.* **9**: 230 (Sept-Oct) 1942.

11 Redisch, W., and Pelzer, R. H. Capillary Studies in Migraine. Effect of Ergotamine Tartrate and Water Diuresis, *Am. Heart J.* **26**: 598 (Nov) 1943.

12 Levinson, J. P., and Essex, H. E. Observations on the Effect of Certain Drugs on the Small Blood Vessels of the Rabbit Ear Before and After Denervation, *Am. J. Physiol.* **139**: 423 (July) 1943.

crease the flow of blood to the extremities. The mechanism of action and the causative factors are still questioned, but the current opinion still favors nicotine and its effect on the sympathetic nervous system. Evans and Stewart¹³ studied this problem and measured the peripheral blood flow by means of a modification of the method of Hardy and Soderstrom. Observations were made on normal persons not only after they had smoked the standard type of cigaret but also after their smoking denicotinized cigaret and cigarets made from cornsilk and after their smoking through a water pipe. A decrease in blood flow occurred in every instance, regardless of the type of cigaret smoked. After the cessation of smoking, the flow usually decreased and by the end of thirty minutes returned to normal. In addition, the blood pressure, pulse rate and rectal temperature increased regardless of the type of cigaret smoked, and the temperatures of the skin of the hands and feet usually decreased. The effects on the basal metabolic rate and on the electrocardiogram were either too slight or too variable to be of significance. Since these changes occurred after the smoking of the cigarets which did not contain nicotine as well as of those which did, it was natural for the authors to conclude that nicotine was not the contributing factor. They suggested that stimulation of the sympathetic nervous system brought about by the irritating effect of smoke on the respiratory tract might be responsible for the changes observed. From the results of this study it appeared that smoking of any type of cigaret, regardless of its nicotine content, should be avoided in the presence of peripheral vascular disease.

Blood Flow—After a unilateral peripheral nerve block for the release of arterial tone, it is not an uncommon observation to note a concomitant vasoconstriction in the opposite extremity, providing adequate dilatation is produced on the paralyzed side. Neumann and his colleagues¹⁴ reiterated this observation and offered a logical explanation. They compared the vascular changes in the small vessels of the toes with those in the fingers following spinal anesthesia. They also compared the changes in the fingers of the two hands following a local block of one stellate ganglion. The pulse wave in the digit devoid of its sympathetic supply increased and the alpha waves decreased, but in the control both waves decreased to one-half or one-

quarter their former size. Measurements were made with the pneumoplethysmograph of Turner. There were no changes in the blood pressure or pulse rate during the period of spinal or regional anesthesia. These phenomena were not noted when occlusive vascular disease was present. The authors considered the mechanism to be one of adjustment, possibly of compensation, through efferent pathways of the sympathetic system. Paralysis of these nerves permitted maximal expansion of the small blood vessels and interrupted the pathways of stimuli necessary for the formation of prominent alpha waves. At the same time, increased sympathetic outflow to certain other vascular fields resulted in vasoconstriction of such intensity as to produce small pulse waves and to inhibit the relaxation apparently necessary for the development of alpha waves.

Stewart and Evans¹⁵ studied the peripheral blood flow under basal conditions in 34 normal men in the third decade of life. Measurements of blood flow were made by a modification of the method of Hardy and Soderstrom. In using this method certain data were required, namely, cutaneous temperatures at 11 points on the anterior surface of the body, rectal temperature, oxygen consumption, height and body weight. The average peripheral blood flow was 52 cc per square meter per minute at 27 C. The flow at room temperatures of 25 C showed a range from 8 to 78 cc per square meter per minute and at 27 from 34 to 127 cc per square meter per minute. The flow usually varied in the same direction as the basal metabolic rate. The blood pressure and pulse rate were normal in each instance, and there were no differences in the averages for the subjects who were studied at 25 C and those studied at 27 C.

The rate and control of blood flow through the skin of the upper extremities were recently computed by Goetz.¹⁶ Studies were performed on 800 persons, and the determinations were made with the optical plethysmograph. This apparatus is similar to the finger plethysmograph described by Johnson. It is extremely sensitive and capable of registering not only the actual volume of the digits (skin) but the shape and height of the individual volume pulse. He found the pulse volume in the digits of normal warm-handed subjects to vary between 0.003 cc during full constriction and 0.025 cc at full dilatation. The height of the pulse volume was considered a more sensitive measure of vasomotor tone and of

13 Evans, W. F., and Stewart, H. J. Effect of Smoking Cigaretts on Peripheral Blood Flow, *Am Heart J* 26: 78 (July) 1943.

14 Neumann, C., Sellers, E. A., Rovenstine, E. A., Cohn, A. E., and Rule, C. Influence of Spinal and Regional Anesthesia upon Vasoconstriction and Vaso-dilatation of Small Peripheral Blood Vessels, *Proc Soc Exper Biol & Med* 53: 159 (June) 1943.

15 Stewart, H. J., and Evans, W. F. Peripheral Blood Flow Under Basal Conditions in Normal Male Subjects in Third Decade, *Am Heart J* 26: 67 (July) 1943.

16 Goetz, R. H. Rate and Control of Blood Flow Through Skin of Upper Extremities, *South African J. M. Sc* 8: 65 (Feb.) 1943.

the potency of the arterial tree than most methods used for similar study. Comparing it with surface temperature, Goetz showed that when the latter reached the normal vasodilating level tracings of the pulse volume might demonstrate a decreased flow indicative of organic vascular disease. The rate of blood flow in the fingers of normal subjects was measured by means of the venous congestion test. This rate varied between 3 cc per minute for 100 cc of tissue during maximal constriction and 94 cc during dilation. The rate of blood flow in the skin of the terminal phalanx was found to exceed that of the skin of the other phalanges.

Barcroft and Edholm¹⁷ described the variations in blood flow of the forearm as a result of changes in temperature of the surrounding water in the plethysmograph. Studies of deep muscle temperature were also performed. Readings were obtained for a two hour period with water temperatures ranging from 13 to 45 C. The average values for blood flow in the forearm ranged from 0.5 cc per hundred cubic centimeters of forearm per minute at 13 C to 17.6 cc at 45 C. The flow-time relations fell into three groups. 1. At 13.0 to 35.0 C there was a slight decrease in flow during the two hour period, which was not conspicuous except in the first fifteen minutes. 2. At 37.0 to 45.0 C the flow increased to a maximum in about one hour and then decreased steadily. 3. At 45 C there was an increase to a maximum in thirty to forty-five minutes and the flow then remained constant. The authors also noted that spontaneous fluctuations in blood flow were more frequent at higher temperatures. The deep muscle temperature taken from the middle of the upper part of the forearm ranged from 18.0 C after two hours' immersion at 13.0 C to 39.0 C after thirty minutes' immersion at 42.5 to 45.0 C.

The blood flow patterns of various arteries were optically recorded by Shipley, Gregg and Schroeder¹⁸ with an improved orifice type flow meter. These patterns were found to be characteristically distinctive of a given artery and its bed. For heteronymous arteries the pattern exhibited wide variations in magnitude, timing, direction and rate of flow but showed similarity of contour to the respective pressure pulses of the arteries. Back flow components existed in the femoral and axillary arterial flow and less frequently in the common carotid pattern, but the renal, hepatic and superior mesenteric

arteries exhibited only a forward flow. This study lends itself to a qualitative evaluation of differences among the flow patterns of the same or of different arteries under various physiologic conditions.

The effect on the peripheral circulation of a period of relative anoxia was studied in a series of 25 normal subjects by Abramson and his associates,¹⁹ using the venous occlusion plethysmograph. Anoxia was obtained by the inhalation of an oxygen-poor gas mixture (10 per cent oxygen and 90 per cent nitrogen) for periods of ten to twenty-seven minutes. During these periods they noted a small but definite increase in the rate at which blood flowed through the forearm and leg and generally a decrease in the circulation in the hand. In view of the fact that the vessels in the hand respond to all types of vasoconstricting stimuli, the results obtained during the period of anoxia were not considered greatly significant. Associated with the increase in the blood circulating through the forearm and leg were a significant augmentation in pulse rate, a slight elevation of systolic blood pressure and variable changes in the rate of respiration. The circulatory response to a period of exercise during the inhalation of the oxygen-poor gas was also compared with that obtained under normal circumstances. The results were interpreted to indicate that the compensatory adjustments to work in a state of relative anoxia were not as adequate as those elicited normally.

Himmelsbach²⁰ studied the blood flow in drug addicts. He used the venous occlusion plethysmographic method of Hewlett and Van Zwaluwenbuig. The resting blood flow to the hands of morphine addicts and former addicts was found to be subnormal, whereas that of marijuana users was normal. Morphine was found to cause a significant increase in the rate of blood flow to the hands of addicts, of former addicts and of normal controls. The total increase to the hand in the first hour after the injection was greater with 10 and 20 mg than with 40 and 60 mg. Demerol hydrochloride (the hydrochloride of the ethyl ester of 1-methyl-4-phenylpiperidine-4-carboxylic acid) also increased the blood flow to the hand. These results are of interest from the vascular standpoint, but the author implied, so far as the addiction problem was concerned, that the former addict was tense and morphine relieved this state through a depression of the sympathetic division of the ner-

17 Barcroft, H., and Edholm, O. G. The Effect of Temperature on Blood Flow and Deep Temperature in the Human Forearm, *J Physiol* **102** 5 (June 30) 1943

18 Shipley, R. E., Gregg, D. E., and Schroeder, E. F. An Experimental Study of Flow Patterns in Various Peripheral Arteries, *Am J Physiol* **138** 718 (April) 1943

19 Abramson, D. I., Landt, H., and Benjamin, J. E. Peripheral Vascular Response to Acute Anoxia, *Arch Int Med* **71** 583 (May) 1943

20 Himmelsbach, C. K. Studies on the Relation of Drug Addiction to the Autonomic Nervous System. Results of Tests of Peripheral Blood Flow, *J Pharmacol & Exper Therap* **80** 343 (April) 1944

vous system. Larger doses tended to evoke counter action.

Studies on the surface temperatures of persons with induced vitamin B deficiencies were recently reported by Roth and her colleagues²¹. These were performed on 8 subjects under controlled environmental, postural and metabolic conditions. In no case did deficiencies in thiamine, riboflavin and other components of the vitamin B complex show any degree of vasomotor disturbances as evidenced by measurements of cutaneous temperature and determinations of rates of cooling and warming of body tissue.

Denervation—Observations were made by Essex and associates²² on the blood flow in the femoral arteries of a dog at intervals over a period of ten years and two months. Blood flow was measured in both femoral arteries simultaneously with the area under infiltration anesthesia before and after sympathetic ganglionectomy and at various times up to ten years and two months thereafter. Whereas the flow was twice as great in the left or sympathectomized limb as it was in the right, or control limb fifteen days and also ten months and twenty-five days after the sympathectomy, the flow was almost the same in the two limbs nine and also ten years after the operation. The vessels of the sympathectomized leg were found to be hypersensitive to epinephrine more than nine and ten years following sympathectomy. This was demonstrated by injecting a small amount of epinephrine hydrochloride, which caused so much constriction of the vessels of the sympathectomized side that the flow was nil for at least two minutes. The flow on the control side determined at the same time was only slightly altered. Simultaneous plethysmographic records of the two hindfeet further confirmed the observations on blood flow, since there was a transient decrease of the volume of the innervated foot but a prolonged decrease of that of the denervated foot in response to small doses of epinephrine. Histologic examination of a toe from each hindfoot showed that the arterioles of the left, or sympathectomized, foot had undergone hypertrophy. This was confined to the muscularis coat of the vessels. The vessels of the control side did not show this change.

21 Roth, G. M., Williams, R. D., and Sheard, C. Skin Temperatures of the Extremities of Persons with Induced Deficiencies of Thiamine, Riboflavin and Other Components of the B Complex, *J Clin Investigation* 23:373 (May) 1944.

22 Essex, H. E., Herrick, J. F., Baldes, E. J., and Mann, F. C. Observations on the Circulation in the Hind Limbs of a Dog Ten Years Following Left Lumbar Sympathetic Ganglionectomy, *Am J Physiol* 139:351 (July) 1943.

Richards²³ reported at length his observations of the vasomotor disturbances in the hand following a division of a peripheral nerve. He used the surface temperature as an index of vasomotor response. The results were divided into two phases: an initial phase of vasodilatation, due to the interruption of the sympathetic vasoconstrictor fibers, and a second, but permanent, phase, in which the temperature of the area approximated that of its environment. There was no clearcut distinction in time between these two phases. Although Richards was unable to understand the factors responsible for the change to the cold phase, he believed that such conditions as lowering of local metabolism, sensitization of denervated blood vessels to circulating epinephrine and loss of afferent nerve fibers responsible for the "axon reflex" probably played a significant role.

Richards also noted that a digit which was incompletely denervated might show an almost normal reflex vasomotor activity, whereas a completely denervated digit does not respond reflexly to changes in body temperature but responds to the local metabolic needs of the tissues. Studies on denervated limbs have been done before, and in general their findings have been in agreement with those of Richards. The exact role played by various nerve structures is not entirely settled. Doupe²⁴ has recently published a series of articles on his observations on subjects with preganglionic and ganglionic sympathectomies and patients with lesions of peripheral nerves. The circulation was evaluated in some with the usual thermocouple and in others with the plethysmograph. Various measures were used to modify the circulation, mainly application of heat or of cold. The digital vascular reactions accompanying lesions of peripheral nerves were found to be similar to those following sympathetic ganglionectomy. The author expressed the belief that the tendency to coldness of completely denervated digits was due to hypersensitivity to the local vasoconstricting action of the sympathetic fibers. The action of cold was made apparent in denervated digits because of the facilities for loss of heat afforded by vasoconstriction in the remainder of the limb, by the action of epinephrine and by the cooling by disuse. After reactive hyperemia the flow of blood to the denervated

23 Richards, R. L. Vasomotor Disturbances in Hand After Injuries of Peripheral Nerves, *Edinburgh M J* 50:449 (Aug) 1943.

24 Doupe, J. Studies on Denervation. A Methods, *J Neurol & Psychiat* 6:94 (July-Oct) 1943, B The Circulation in Denervated Digits, *ibid* 6:97 (July-Oct) 1943, D The Mechanism of Axonal Vasodilatation, *ibid* 6:115 (July-Oct) 1943, E Observations Concerning Adrenalin, *ibid* 6:121 (July-Oct) 1943.

digit was commensurate with the needs of the tissues. Doupe concluded by stating the belief that no correlation exists between Raynaud's syndrome and denervation sensitivity, in that the blood flow to the tissues in the presence of lesions of a peripheral nerve is adequate to the needs of the tissue, while with Raynaud's syndrome ischemia occurs. He also expressed the view that the effect of temperature on the vessels is dependent on changes of p_H and resulting changes in metabolism of the tissue. Lowering of the temperature decreases the formation of acid metabolites and so indirectly leads to an elevation of p_H and vasoconstriction. The opposite occurs with heat.

Doupe presented a case report supporting in part the theory of Lewis that the fibers concerned in axonal vasodilatation belong to the posterior root but are not afferent fibers. In his case the ulnar nerve had been sectioned and the median nerve was found to have an unusual distribution. Evidence was presented to show that axonal vasodilatation was mediated in part by fibers other than those associated with sensation. In contrast to the view of Lewis, this author expressed the belief that potent vasodilating substances might be liberated from nerve fibers near their termination.

The same author reported the effects of injections of epinephrine hydrochloride on the circulation of denervated digits and observations indicating the release of natural epinephrine. Like others, he found the vessels of denervated digits with associated degeneration of their sympathetic fibers to have a lowered threshold and a prolonged response to the action of epinephrine, whereas the vessels in preganglionectomized digits showed only a lowered threshold. Conflicting results were obtained concerning the function of epinephrine in regulation of temperature, but the author inferred that the need for conservation of heat did not consistently evoke the secretion of epinephrine. The latter was also true in peripheral neurogenic vasoconstriction. Epinephrine was capable of being liberated in the body in amounts comparable to the intravenous injection of 20 micrograms and for longer periods at the rate of 60 micrograms per minute. He finally considered that under other circumstances much larger amounts might be liberated and would suffice to initiate a persistent vasoconstriction in a denervated digit.

Potassium—Rewell²⁵ reported a significant elevation of serum potassium after the removal of a tourniquet applied to a limb during the course

of various orthopaedic procedures. Twelve cases were studied, and the period of ischemia lasted from thirty-five to one hundred minutes. This study lends support to the contention that potassium plays a major role in the production of pain during ischemia. Rewell suggested that the extra potassium in the circulation might come from the ischemic area but that it might also originate in the liver by the action of a hypothetical substance released in the limb.

Anticoagulants—The popularity of dicoumarin (3,3'-methylenebis-[4-hydroxycoumarin]) and heparin is evident from the increasing number of publications about them. From these a few have been selected for presentation here. A collective review on these preparations was presented by Pfeiffer and Sam²⁶.

Attempts are being made to prolong the action of heparin, which would eliminate one of its chief disadvantages. Loewe, Rosenblatt and Lederer²⁷ administered the drug in the Pitkin menstruum and found this mixture capable of prolonging the coagulation time in rabbits. The effects of a single dose lasted from twenty-four to as much as seventy-two hours. In several animals heparinization was initiated with 50 mg of heparin in this menstruum and continued as required with 25 mg doses. In this manner it was possible to maintain adequate heparinization over a two week period with a total dose of 100 mg. This can be contrasted with a two week requirement of 630 mg of commercial heparin given subcutaneously in fractional daily doses of about 45 mg. The authors expressed the opinion that by further revamping the mixture a more prolonged absorption might occur.

Bryson²⁸ was also able to prolong the anticoagulant action of heparin by suspending it in a beeswax-sesame oil mixture. For proper suspension the heparin was finely powdered. Studies were performed on dogs. After injections of 100 to 150 mg of heparin in 0.5 to 1.5 cc of the beeswax mixture, the coagulation time of the blood was increased for periods which ranged from seventeen to seventy hours. In most instances the coagulation time during these periods was within satisfactory therapeutic limits. Judd, in discussing this method of administration, reported its effect on 5 patients. Two hundred milligrams of heparin in 2 cc of the 10 per cent mixture of beeswax was injected

26 Pfeiffer, D. B., and Sam, F. D. Heparin and Dicoumarol, *Internat Abstr Surg* 78:109 (Feb) 1944.

27 Loewe, L., Rosenblatt, P., and Lederer, M. A New Method of Administering Heparin, *Proc Soc Exper Biol & Med* 50:53 (May) 1942.

28 Bryson, J. C., and Code, C. F. Prolonged Anticoagulant Action of Heparin in a Beeswax Mixture, *Proc Staff Meet, Mayo Clin* 19:100 (Feb 23) 1944.

25 Rewell, R. E. Rise in Potassium Concentration in Blood Stream Following Ischemia of Muscle Masses, *Brit M J* 2:483 (Oct 16) 1943.

intramuscularly in most of the patients. The injection was harmless, and an elevation in the clotting time of the blood was produced in each case. The peak of the reaction was reached in twenty-four hours, at which point a "plateau" developed and was maintained for from three to five days. This series is unfortunately too small to permit any definite conclusions.

The synergistic action of heparin and dicoumarin was recently studied by Walker and Rhoads²⁹. They reported that under controlled conditions the action of heparin was enhanced by dicoumarin when the prothrombin time was depressed to 20 or 30 per cent of normal by the action of the latter drug. From one half to one third of the usual amount of heparin was needed to produce a given effect in the subjects treated with dicoumarin. This is not unreasonable when one considers that dicoumarin reduces prothrombin and that the susceptibility to the action of heparin is related to the amounts of prothrombin and thrombin in circulation. From a clinical standpoint the importance of this observation is questioned, as the drugs are seldom used together except when quick anticoagulant action is desired, and under these circumstances for a few days only.

Meyer and Spooner³⁰ found that dicoumarin was absorbed when administered rectally and produced effects similar to those resulting from oral or intravenous exhibition of the drug. There was no change in the latent period by this method of administration. It was inserted either in an aqueous suspension or in a cocoa butter suppository.

McCarter and his colleagues³¹ administered various doses of dicoumarin to a series of 29 dogs. The amount administered was far larger than necessary for therapeutic purposes. The animals were killed and the following outstanding morphologic evidences of poisoning were noted: toxic lesions of the small blood vessels sufficient to make hemorrhages almost inevitable, acute renal glomerular swelling and a toxic reaction in the lymphoid tissues. No necrosis of the liver and no consistent hepatic degenerative lesions were found. In 6 dogs receiving dicoumarin at therapeutic levels of dosage, one mild lymphoid tissue reaction was noted.

Autopsies performed on 5 human beings with a variety of diseases who were receiving dicoumarin at the time of death revealed none of the toxic changes just described. In several instances a mild lymphoid reaction could be detected.

Cahan³² described a patient who received 2,800 mg of dicoumarin in thirty-two days and had hemorrhagic and purpuric manifestations. There were an associated prolongation of the bleeding time and a pronounced deficiency of prothrombin without reduction in platelets, capillary fragility or abnormality in clot retraction. This patient had received dicoumarin in almost daily doses of 100 mg during the thirty-two days before he came to the author as a patient. Cahan concluded that toxicity caused by dicoumarin induces not only hypoprothrombinemia but an increased sensitivity of the vascular bed to trauma. This conclusion was derived from the behavior of the skin following a needle puncture tourniquet test.

Lucia and Aggeler³³ recommended vitamin K₁ oxide as a means of treating dicoumarin-induced hemorrhages. He was able to elevate the prothrombin concentration in the blood of a man who had received large doses of dicoumarin by the intravenous injection of 500 mg of vitamin K₁ oxide. The period elapsing between the institution of treatment with vitamin K₁ oxide and the cessation of the hemorrhagic phenomena was too long to make the method entirely satisfactory.

Morton and co-workers³⁴ have performed a group of experiments to study the possible influence of vitamin K on thrombus formation in dogs. The radial and saphenous veins of the legs of 52 dogs were traumatized mechanically by scarifying the intima with a hooked needle. The veins were removed at forty-eight and ninety-six hour intervals afterward. Twenty-seven of the animals received a surplus of synthetic vitamin K along with the regular diet for a week prior to the injury, and the remaining 25 were utilized as controls. Determinations of prothrombin and clotting times as well as hematocrit determinations were made at intervals on each animal without demonstrating any effect of the administration of synthetic vitamin K.

29 Walker, J., and Rhoads, J. E. Effect of Dicoumarol on Susceptibility to Action of Heparin, *Surgery* **15** 859 (May) 1944.

30 Meyer, O. O., and Spooner, M. The Rectal Administration of Dicoumarol, *Proc Soc Exper Biol & Med* **54** 88 (Oct) 1943.

31 McCarter, J. C., Bingham, J. B., and Meyer, O. O. Studies on the Hemorrhagic Agent 3,3'-Methylenbis (4-Hydroxycoumarin). IV. The Pathologic Findings After the Administration of Dicoumarol, *Am J Path* **20** 651 (May) 1944.

32 Cahan, A. Hemorrhage and Purpura Caused by Dicoumarin, *New England J Med* **228** 820 (June) 1943.

33 Lucia, S. P., and Aggeler, P. M. Treatment of Dicoumarol-Induced Hypoprothrombinemic Hemorrhage with Vitamin K₁ Oxide, *Proc Soc Exper Biol & Med* **56** 36 (May) 1944.

34 Morton, C. B., Shearburn, E. W., and Burger, R. E. Synthetic Vitamin K and the Thrombosis of Veins Following Injury, *Surgery* **14** 915 (Dec) 1943.

The incidence of thrombosis after injury to the intima of the veins was not significantly increased coincident with the administration of synthetic vitamin K, being 33.0 per cent in the control group and 38.0 per cent in the group given the vitamin K preparation. The small difference was not considered important. The prothrombin values did not significantly change after the administration of synthetic vitamin K. There was no significant difference in the results obtained with synthetic preparations from two different manufacturers. The dogs with a hematocrit reading below 40 per cent, however, revealed a slightly higher incidence of thrombosis in both the control and the vitamin K-fed group.

Clinically, the incidence of thrombophlebitis was less in a small group of women given synthetic vitamin K just before or at the time of delivery than in a larger group receiving no exogenous vitamin K except in the normal diet.

Different results were obtained by Rabinovitch and Pines³⁵ with heparin. They were able to produce local clot formation in the veins of rabbits by a forcible pull on the vein followed by partial constriction at the site of injury. When heparin was administered even in small doses before injury of the vein and formation of a thrombus, it prevented the subsequent development of a local intravascular clot. The authors also found it unnecessary in their experiments to administer the anticoagulant continuously in order to obtain the desired effects of the drug. In a certain number of animals, heparin proved effective in causing the solution or disappearance of a thrombus, but only when given during the early stages of clot formation. It had no effect when given after the clot had already organized.

Shapiro, Redish and Campbell³⁶ administered dicoumarin to 18 patients with hepatic disease and hypoprothrombinemia. The dose selected was 50 mg, as this amount was considered one-half the minimal dose capable of prolonging the prothrombin time in normal persons. All of the patients with Laennec's cirrhosis with marked or moderate preexisting prolongation of the diluted plasma prothrombin time showed a definite response to the smaller dose of dicoumarin. Of the 6 patients with slightly prolonged diluted plasma prothrombin time, 3 showed further increase, while those with an

initial normal prothrombin time did not respond to dicoumarin. In those in which prolongation did occur the time of the first detectable change was the same as in normal persons.

Wasserman and Stats³⁷ found that dicoumarin produced a variable response in 71 adult patients. The drug was administered in the usual manner. They expressed the belief that patients receiving this drug must be individualized, as a fixed dosage schedule cannot be made. Of the 8 patients in whom hemorrhages developed, one died. The authors did not elucidate on this patient's case, but it was noted that his prothrombin time was 7 per cent at the time of bleeding. This occurred at the site of an amputation and from the rectum. In 4 other cases transfusions of fresh blood did not arrest the hemorrhagic tendency due to dicoumarin. Several instances were reported in which embolism, thrombosis or progression of existing venous thrombosis occurred despite a low blood prothrombin. The drug failed to produce symptomatic improvement in 10 cases of occlusive peripheral vascular disease during a three month trial. The authors concluded that dicoumarin needs further trial before its effects in cases of peripheral venous thromboses and of pulmonary infarction can be determined.

Evans³⁸ also emphasized the dangers and disadvantages of dicoumarin, but in his opinion the obvious advantages so far outweigh the dangers of this preventive method if adequate laboratory facilities and proper precautions are observed. Fifty-six patients were treated with dicoumarin alone or with dicoumarin combined with heparin. Of the 4 deaths that occurred, 2 were ascribed directly to dicoumarin poisoning and hemorrhage. Hemorrhagic phenomena were evident in 8 cases (14 per cent). Evans reemphasized the principal precaution in administration of dicoumarin, namely, to determine the morning prothrombin time before ordering the daily maintenance dose. The combined use of heparin and dicoumarin was considered safe only if the doses of heparin were controlled by determinations of the prothrombin time twice daily.

ATHEROSCLEROSIS

The current literature again stresses the importance of the lipids in the causation of atherosclerosis. An excellent review on this subject was recently presented by Hirsch and Wein-

35 Rabinovitch, J, and Pines, B. Effect of Heparin on Experimentally Produced Venous Thrombosis, *Surgery* **14** 669 (Nov) 1943.

36 Shapiro, S, Redish, M. H, and Campbell, H. A. Studies on Prothrombin. II. The Effects of a Single Small Dose of Dicumarol (3,3'-Methylenebis [4-Hydroxycoumarin]) in Liver Disease, *Am J M Sc* **205** 808 (June) 1943.

37 Wasserman, L. R, and Stats, D. Clinical Observations on the Effect of 3,3'-Methylenebis (4-Hydroxycoumarin), *Am J M Sc* **206** 466 (Oct) 1943.

38 Evans, J. A. Dicumarol Therapy in Thrombotic Emergencies, *New England J Med* **230** 131 (Feb 3) 1944.

house³⁹ The evidence presented in their review favors the opinion that atherosclerosis develops from disturbances in the metabolism of lipids which have infiltrated into the tissues of the intima

Dauber and Katz⁴⁰ reported additional information on the production of atherosclerosis in the chick with cholesterol By controlled experiments they eliminated the factor of cottonseed oil and simple underfeeding in the production of atheroma Forty-three 3 month old cockerels were divided into four groups One group received liberal amounts of an adequate diet for six months The second group received the same diet plus cottonseed oil The third group was placed on a regimen of restricted feeding, and the fourth group received the basic mash plus 2 per cent cholesterol in cottonseed oil Every cholesterol-fed chick acquired atherosclerosis of the thoracic and the abdominal aorta and of their major branches Atheroma was not present in any of the other groups, but the cockerels not fed cholesterol showed a high incidence of intimal fibrosis of the abdominal aorta with or without lipid The authors considered the latter pathologic change as an early spontaneous vascular lesion, but in no instance was foam cell atheroma or calcification noted

Holman⁴¹ confirmed previous work on the experimental production of a necrotizing arteritis in hypertensive dogs with renal insufficiency and also noted that by controlling the diet these lesions were produced with a greater degree of regularity This was demonstrated by the observation that typical arterial lesions developed in only 52 per cent of the hypertensive dogs receiving the regular kennel diet, whereas such pathologic changes developed in 88 per cent of the animals which were fed a specially prepared diet The latter consisted of calves' liver, cane sugar, corn starch, butter, cod liver oil, a salt mixture, kaolin and tomato juice It was found necessary to feed this diet prior to the production of renal insufficiency Certain other factors were found to influence the development of these lesions Citrate and homologous plasma augmented their production, and a saline-citrate solution not only prevented their occurrence but also protected the dogs against death

39 Hirsch, E F, and Weinhouse, S The Role of the Lipids in Atherosclerosis, *Physiol Rev* **23** 185 (July) 1943

40 Dauber, D V, and Katz, L N Experimental Atherosclerosis in the Chick, *Arch Path* **36** 473 (Nov) 1943

41 Holman, R L Necrotizing Arteritis in Dogs Related to Diet and Renal Insufficiency V Evidence for a Dietary Factor, *Am J Path* **19** 977 (Nov) 1943

after a dose of uranium nitrate which had previously proved lethal to 12 of 13 control animals The author concluded that if a dietary factor was involved in the production of arterial lesions it manifested itself only in the presence of renal insufficiency

Bruger, Wright and Wiland⁴² continued their studies on the effect of testosterone propionate and estradiol dipropionate on the cholesterol content of the blood and of the aorta in female rabbits fed cholesterol Previous studies had shown that these hormones inhibited the development of hypercholesteremia and prevented disposition of cholesterol in the aorta The additional studies were done on castrated female rabbits Testosterone propionate and estradiol dipropionate failed to inhibit the hypercholesteremia and excess deposition of cholesterol in the aortas of the animals that were fed cholesterol, in contrast to its protective action in the normal female rabbit Control studies revealed that the presence or absence of the female gonad had little influence on the cholesterol content of the blood or of the aorta, normally or after feeding of cholesterol

An uncommon lesion of smaller arteries was recently described by Sheehan⁴³ They were found in organs subjected to roentgen therapy They consisted of a plaque-like thickening of the intima due to a collection of foam cells alone or of foam cells mixed with various other cells, fluid, fibrin or hyaline material This was most pronounced between the endothelium and the internal elastic membrane Occasional changes were noted in the adjacent internal elastic membrane, media and adventitia These plaques caused a narrowing of the lumen or even occlusion Thrombosis, fibroblastic proliferation of the intima or deposition of elastic tissue in the thickened intima seldom occurred The author expressed the opinion that irradiation of the endothelial cells causes not only morphologic changes but also sufficient change in their permeability to permit red cells, as well as lymphocytes and monocytes, to pass through and accumulate in the intima The disintegration of the red cells or of thrombi in the intima liberates a lipid substance which is subsequently phagocytosed by monocytes and converted into foam cells These foam cells closely resemble the early lesions of atherosclerosis

42 Bruger, M, Wright, I S, and Wiland, J Experimental Atherosclerosis, *Arch Path* **36** 612 (Dec) 1943

43 Sheehan, J F Foam Cell Plaques in the Intima of Irradiated Small Arteries (100 to 500 Microns in External Diameter), *Arch Path* **37** 297 (May) 1944

EMBOLISM AND THROMBOSIS

Spiegel, Friedlander and Silbert⁴⁴ attempted to prevent gangrene in the limbs of cats and dogs by autotransfusion proximal to the site of occlusion. Sufficient ischemia with resulting gangrene was produced by several procedures. Bilateral ischemic paralysis and gangrene of the lower extremities in cats were produced in 10 of 12 experiments in which the three terminal branches of the abdominal aorta and the anastomotic branches of the femoral arteries were ligated. Unilateral ischemic paralysis and gangrene of the lower extremity were produced in cats in 4 of 5 experiments in which the middle hemorrhoidal, the common iliac and the homolateral anastomotic branches of the femoral artery were ligated. In 3 of 6 experiments on dogs, gangrene of the lower extremities was produced by ligating the three terminal branches of the aorta. The authors then transfused the artery proximal to the ligation, and in some experiments pulsations in the vessels returned for several hours. The blood was obtained from donor arteries and in other cases from the abdominal venous reservoir. Even though many failures were encountered and the results none too conclusive the experiments were of interest and worthy of mention.

Eight additional cases of gangrene of the finger following a digital nerve block were described by O'Neil and Byrne⁴⁵. Although the exact cause for this complication is not known, the authors believed that the injected solution may interfere with the digital circulation and produce gangrene if too much solution is injected, if epinephrine is present in the solution or if tourniquets are used. They also considered the possibility of minimal circulatory damage being aggravated by subsequent soaking of the finger in water sufficiently warm to hasten devitalization of the tissue. They suggested that digital nerve block be replaced whenever possible by general anesthesia. If this is not feasible small quantities of an epinephrine-free solution should be used without the aid of a tourniquet.

Gangrene as a complication of an infectious disease is uncommon, and only 1 or 2 cases are reported each year. Scarlet fever is the most common offender and children the victims. An interesting series of 3 cases was reported by

Kahn and Heubi⁴⁶. The patients were all children from one family who contracted scarlet fever during the same season. All had complicating peripheral thrombosis and 2 of the 3 children subsequently died. Levin and McElroy,⁴⁷ also described a case of thrombosis of the right axillary artery following cerebrospinal fever. Gangrene developed and ultimately required amputation.

A case of quadrupedal gangrene in a woman of 25 was reported by Fusco and Kell⁴⁸. It was considered to be of syphilitic origin, as no other etiologic factor could be found. Oppenheim and Cohen⁴⁹ reported a case of localized gangrene on the hip of a syphilitic patient following an intramuscular injection of mercuric salicylate. They attributed the gangrene to an arterial embolus produced by the crystals of the insoluble mercuric salicylate injected accidentally into a small artery.

Studies on a case of symmetric gangrene of the tips of the extremities due to cold hemagglutination were reported by Stats and Bullowa⁵⁰. The patient was a 64 year old American Negro in whom gangrene developed after moderate exposure to cold. There was no evidence of peripheral vascular disease. Hemoglobinuria was present. No cause could be found to explain the presence of the cold hemagglutinin. There was no evidence of syphilis or hemolytic anemia. The authors were able to demonstrate the presence of localized hemoglobinemia by exposing one limb to cold. Hemagglutination was also produced in the capillaries of the conjunctiva by similar exposure.

THROMBOANGITIS OBLITERANS

Only a few articles on this disorder came to our attention during the past year. Cases of thromboangitis obliterans in women were described by Le Febvre and Burns⁵¹ and Atlas⁵².

46 Kahn, A. J., and Heubi, J. E. Postscarlet Fever Thromboses, *Quart Bull Indiana Univ M Center* **5** 68 (July) 1943.

47 Levin, A., and McElroy, D. M. A Case of Cerebrospinal Fever with Thrombosis of the Right Axillary Artery Followed by Gangrene of the Right Arm, Necessitating Amputation, *Brit J Surg* **31** 246 (Jan) 1944.

48 Fusco, E. M., and Kell, T. Luetic Quadrupedal Gangrene. Unusual Case, *Virginia M Monthly* **70** 611 (Dec) 1943.

49 Oppenheim, M., and Cohen, D. Local Arterial Embolism, *Arch Dermat & Syph* **49** 219 (March) 1944.

50 Stats, D., and Bullowa, J. G. M. Cold Hemagglutination with Symmetric Gangrene of the Tips of the Extremities, *Arch Int Med* **72** 506 (Oct) 1943.

51 Le Febvre, F. A., and Burns, J. Thromboangitis Obliterans in Women, *Cleveland Clin Quart* **11** 49 (April) 1944.

52 Atlas, L. N. Case of Buerger's Disease in Old Woman, *Am Heart J* **26** 120 (July) 1943.

44 Spiegel, R., Friedlander, M., and Silbert, S. Prevention of Gangrene Following Ligation of Major Arteries. Experimental Study, *Surg, Gynec & Obst* **77** 162 (Aug) 1943.

45 O'Neil, E. E., and Byrne, J. J. Gangrene of Finger Following Digital Nerve Block. Report of Eight Cases with Discussion of Gangrene Pathogenesis. *Am J Surg* **64** 80 (April) 1944.

The patient reported on by the latter author was a 68 year old woman, and pathologic studies confirmed his diagnosis. Of additional interest was the fact that she reached the age of 68 before the peripheral vascular disturbance manifested itself clinically.

Edwards and Edwards⁵³ reported on the pathologic changes in the venous valves in thromboangitis obliterans. These valves were found to be extensively and seriously damaged. The lesions resembled those found elsewhere in the vascular tree, namely, inflammation, thrombosis and dilatation secondary to the obstruction by these processes. Either the valves were disrupted by the inflammatory process, or their excursion was limited by the extent of involvement on the valve itself or on the adjacent vessel wall. Adhesions were also noted. In obstructive thrombosis the valve was destroyed by the organization and recanalization. In mural thromboses the cusps were incorporated in the organizing tissue or their excursion was limited by thickening and adhesions. The dilatation of the veins distal to areas of obstruction was associated with a relative incompetence of the valve. The growth of the reparative tissue frequently added to the thickness and subsequent rigidity of the cusps.

ARTERIOVENOUS FISTULA

Barber and Madden⁵⁴ reported on the spontaneous closure of an arteriovenous fistula in a 24 year old Negro who had been stabbed in the groin. This development tends to support those who advocate a short period of conservative management prior to operation.

PERIARTERITIS NODOSA

During the past year an increasing number of articles were published on this disease. The majority are concerned with the etiology, favoring to a greater extent the theory that periarteritis nodosa is a definite vascular reaction to some allergic mechanism. Case reports are not included in this review, only cases which contribute new information to the problems concerned with this disease are considered.

Rich⁵⁵ reported on a series of 5 patients in whom vascular lesions characteristic of periarteritis nodosa followed hypersensitive reactions

prior to death. These reactions followed therapeutic injections of foreign serum. Four of these patients had received sulfonamide compounds, but in at least 2 the evidence indicated that the hypersensitive reaction was serum sickness and not drug sensitivity. Similar changes were seen in a biopsy specimen of muscle from a patient who had a hypersensitive reaction following treatment with foreign serum and a sulfonamide compound and in the viscera of a patient who had received prophylactic treatment with sulfathiazole against aspiration pneumonia. None of these patients had any symptoms suggestive of periarteritis nodosa prior to the terminal acute illness for which the serum or sulfonamide compound was administered. The vascular lesions appeared to be fresh. From these observations Rich concluded that the vascular lesions of this type could be a manifestation of an anaphylactic type of hypersensitivity. Continuing his studies in the laboratory, Rich and Gregory⁵⁶ established in rabbits a condition analogous to serum sickness in man and produced experimentally typical diffuse periarteritis nodosa. Acute diffuse glomerulonephritis was also noted in a number of animals which had a hypersensitive reaction to the foreign serum. The continued administration of foreign serum or a sulfonamide compound after a hypersensitive reaction had occurred or the injection of a single large amount of foreign serum increased the danger of producing the vascular damage by prolonging the contact of the sensitized body with the offending antigen. The authors suggested as a result of their observations that an attempt should be made to discover and eliminate any inciting antigen in cases of periarteritis nodosa which come under clinical observation.

Harkavy⁵⁷ also presented evidence supporting the role of hypersensitivity in periarteritis nodosa. This author has been following 16 cases of bronchial asthma since 1936, 8 of which have been previously recorded. The necropsy observations on 4 of these patients were described. In 2 the basic vascular lesion was similar to periarteritis nodosa. All of the patients showed evidence of a polyvalent sensitivity of bacterial and nonbacterial origin. The simultaneous precipitation of both the asthma and the polymorphous vascular reaction in these cases by the same allergenic stimulation led Harkavy to conclude (1) that bronchial asthma is fundamentally an expression of hyperergic vascular response.

53 Edwards, E. A., and Edwards, J. E. The Venous Valves in Thromboangitis Obliterans, *Arch Path* **35** 242 (Feb) 1943.

54 Barber, R. F., and Madden, J. L. Spontaneous Closure of Arteriovenous Fistula, *Arch Surg* **47** 364 (Oct) 1943.

55 Rich, A. R. The Role of Hypersensitivity in Periarteritis Nodosa, *Bull Johns Hopkins Hosp* **71** 123 (Sept) 1942.

56 Rich, A. R., and Gregory, J. E. The Experimental Demonstration that Periarteritis Nodosa Is a Manifestation of Hypersensitivity, *Bull Johns Hopkins Hosp* **72** 65 (Aug) 1943.

57 Harkavy, J. Vascular Allergy III. *J Allergy* **14** 507 (Nov) 1943.

which may be reversible or irreversible and (2) that the accompanying resultant pathologic changes in the vessels do not represent disease entities but rather are qualitative and quantitative degrees of hyperergic and anergic responses. He believed that these vascular reactions should be attributed to an allergic mechanism.

In contrast to the work of the previous authors, McCall and Pennock⁵⁸ presented evidence in favor of the toxic origin of periarteritis nodosa. They drew their conclusions from ante-mortem studies in 10 cases of this disease. They were unable to correlate the pathologic changes with preceding therapy with sulfonamide compounds. Although all organs were involved, impairment of the renal functioning tissue was the most constant feature of this syndrome. The authors expressed the belief that the arterial lesions pointed either to a disease of the blood vessels caused by a specific bacterial agent or to a specific vascular reaction to some unidentified toxin or other harmful mechanism.

Boyd⁵⁹ discussed the cerebral and ocular manifestations of periarteritis nodosa, citing many examples from the available literature. In his opinion the ocular lesions are not distinctive, since the retinal changes cannot be distinguished from hypertension, nephritic syndromes and chronic sepsis. Gaynon and Asbury⁶⁰ came to the same conclusion in reporting a case of periarteritis nodosa in which failing vision due to a retinopathy typical of malignant hypertension was the first symptom.

Three interesting cases of polyarteritis nodosa were described by MacKeith⁶¹. All of the patients presented a localized soft pitting of the skin of one or more limbs together with asymmetric muscular weakness. The diagnosis was made during life and confirmed by biopsy.

Guion and Adams⁶² reported the clinical, laboratory and autopsy observations in 6 cases of disseminated lupus erythematosus. Of interest in this review is the observation that although vascular lesions were noted none resembled periarteritis nodosa.

58 McCall, M., and Pennock, J. W. Disseminated Necrotizing Vascularitis. The Toxic Origin of Periarteritis Nodosa, *Am J M Sc* **206** 652 (Nov) 1943.

59 Boyd, L. J. The Cerebral and Ocular Manifestations of Periarteritis Nodosa, *Bull New York M Coll, Flower & Fifth Ave Hosps* **6** 130 (Oct) 1943.

60 Gaynon, I. C., and Asbury, M. K. Ocular Findings in a Case of Periarteritis Nodosa, *Am J Ophth* **26** 1072 (Oct) 1943.

61 MacKeith, R. Localized Subcutaneous Oedema with Weakness of Limb Muscles. A Syndrome Due to Polyarteritis Nodosa, *Brit M J* **1** 139 (Jan 29) 1944.

62 Guion, C. M., and Adams, E. C. Six Autopsied Cases of Disseminated Lupus Erythematosus, *Am J M Sc* **205** 33 (Jan) 1943.

TEMPORAL ARTERITIS

The view that temporal arteritis is a local manifestation of a generalized arterial disease gained support by a recent case report of Chasnoff and Vorzimer⁶³. In their case the patient appeared to be improving from this disease when she suddenly felt severe pain in the head, vomited, lapsed in a stupor and died. The diagnosis, originally made by biopsy, was confirmed by autopsy. Changes similar to those in the temporal arteries were found in other vessels. A complete pathologic report was withheld pending a future publication.

The findings in the eyes in a previously reported case of temporal arteritis were submitted by Post and Sanders⁶⁴. From their own experience and information obtained from the literature, they concluded that ocular lesions frequently accompany temporal arteritis. These lesions consist mainly of an occlusion of the central retinal artery or other large arteries and a localized arterial lesion with hemorrhages or exudates.

AINHUM

Two additional cases of anihum were described by Shearer⁶⁵ and Ussery⁶⁶. The latter author also presented an excellent review of the literature on this disease. In his opinion it is a disease which is almost exclusively found in dark-skinned races, as it has been observed among white persons in only 4 cases. Heredity does not play a role in its production, and consequently it must not be confused with congenital amputation. It consists in spontaneous amputation of the little toe by an adventitious fibrous band. The author stressed the relationship of the disease to leprosy and to a lesser degree to scleroderma, syphilis, larvae and atavism.

GLOMUS TUMOR

That a glomus tumor may develop at any site was recently emphasized by Cloward and Tilden⁶⁷. They reported a case in which a tumor on the wrist followed local trauma. Love⁶⁸ in reporting a case of subungual glomus tumor,

63 Chasnoff, J., and Vorzimer, J. J. Temporal Arteritis. A Local Manifestation of a Systemic Disease, *Ann Int Med* **20** 327 (Feb) 1944.

64 Post, L. T., and Sanders, T. E. Temporal Arteritis. Case Report with Eye Findings, *Tr Am Ophth Soc* **41** 241, 1943.

65 Shearer, W. S. Ainhum, *Brit J Radiol* **17** 25 (Jan) 1944.

66 Ussery, G. C. Ainhum. Review and Case Report, *J M A Alabama* **13** 319 (April) 1944.

67 Cloward, R. B., and Tilden, I. L. Glomus Tumor of the Wrist, *Hawaii M J* **2** 299 (July-Aug) 1943.

68 Love, J. G. Glomus Tumors, *Proc Staff Meet, Mayo Clin* **19** 113 (March 8) 1944.

described a "pin test" which was of value in localizing the tumor. After the patient's confidence had been gained, the point of a steel pin was pressed into the skin to within 1 cc of the lesion without producing severe pain, but just as soon as the point was pressed over the lesion excruciating pain developed.

VASOSPASTIC DISORDERS

Immersion Foot—This condition was described in detail in a previous review. Of the recent articles, only those with additional information are included at this time. An interesting discussion on injuries due to immersion and vasomotor disorders in wartime was noted in the *Proceedings of the Royal Society of Medicine*⁶⁹. Learmonth was the first participant and classified the vasomotor disorders resulting from injury in patients with peripheral vascular disease and those resulting from the local effects of cold. Case histories were described in each group. Ungley and Greene reiterated the subject of immersion foot. Of interest was an abstract by Blackwood, who recorded histologic and experimental observations. The human material which was studied consisted of one foot from a man who died half an hour before rescue and of tissues from extremities of survivors amputated within two to twenty-six months after rescue. In the majority of cases peripheral sepsis was present. The histologic appearance suggested that at the time of immersion damage was done to all the structures in the limb, of a degree and to a level dependent on the length and severity of exposure. Damage to nerves and muscle was striking. The nerves had the greater proportion of their axicylinders and myelin sheaths destroyed. Muscular damage appeared to be due to trauma. Hemorrhage from and thrombosis of veins and venules were noted. All of these changes were patchy but became more marked peripherally. Regeneration of the nerves was noted after rescue. Blackwood's original article⁷⁰ was recently obtained and found to contain a more detailed description of the pathologic changes in this disorder. His photographs are worthy of commendation.

Experimental studies of immersion foot were also conducted by Blackwood and Russell⁷¹. They made a histologic study of the changes

occurring in the tail of the rat after periods of exposure to cold and wet. The periods and conditions of exposure were comparable to those under which the less severe forms of immersion foot developed in man. This was accomplished by allowing cold artificial sea water to trickle slowly through the bottom of their cages. The depth of water never exceeded $\frac{1}{2}$ inch (1.3 cm), and the animals were kept in a cold room. The period of exposure varied but seldom exceeded ninety-six hours. On release, some of the animals were allowed to recover slowly, others were warmed up rapidly, and the remaining group were immediately placed in a hot air incubator at 37 C. Conspicuous damage to the muscle and nerve tissue was found to be present after exposures of forty-eight hours. This increased with longer exposures. The skin and other tissues, including blood vessels, appeared much more resistant to chilling. In some of the animals which had been killed two months after exposure the nerve and muscle tissue had not returned to normal, and in others muscle degeneration secondary to denervation was already present. Treatment in the form of the two heating-up processes was found to accelerate the initial reaction, but it made no significant difference in the histologic changes after one month.

It is now well established that in the therapy of immersion foot the extremity must be kept in a cool environment. Ungley⁷² was able to accomplish this by exposing the feet of 2 victims to a cool room temperature and having an electric fan play on the soles of the feet. The speed and distance of the fan were adjusted to maintain cutaneous temperatures of 23 to 26 C (73.4 to 78.8 F). Cooling to less than 21 C (69.8 F) gave rise to discomfort.

Frostbite—Greene⁷³ recently reviewed the experimental work on frostbite and reported his results with the albino mouse. This animal was selected because of its convenient size and the standard length of its tail. The mouse was placed in a tube with its tail in a separate compartment which contained solid carbon dioxide at a temperature of —62 to —67 C. The degree of frostbite depended entirely on the length of time of exposure. Greene selected one minute and then observed the resultant damage for many days, reporting his observations at various intervals. Early gangrene of the tip was noted at the end of the first day, it had become dry at the eighth day and was self amputating from this time up to the eighteenth day. Studies

69 Discussion on Immersion Injuries and Vasomotor Disorders of Limbs in Wartime, Proc Roy Soc Med 36 515 (Aug) 1943

70 Blackwood, W. Studies in the Pathology of Human "Immersion Foot," Brit J Surg 31 329 (April) 1944

71 Blackwood, W, and Russell, H. Immersion Foot, Edinburgh M J 50 385 (July) 1943

72 Ungley, C C. Immersion Foot Treatment by Dry Cooling, Lancet 1 681 (May 29) 1943

73 Greene, R. Immediate Vascular Changes in True Frostbite, J Path & Bact 55 259 (July) 1943

were performed on a smaller group of mice with a longer period of exposure. The studies revealed that in the presence of necrosis the arteries were damaged, with a "silting up" of vessels with cells. In that part of the tail destined to recovery no constant change other than an initial vasoconstriction followed by vasodilatation was observed. This part of the tail had originally been frozen to solidification, as had the adjacent tissue, which became gangrenous. In no case did he find signs of thrombosis in the tails subjected to dry cold. The essential change was a loss of fluid from the blood vessels. Occasionally, damage was so severe that whole blood was lost. Usually only plasma was lost, corpuscles being left stranded within the vessels, which in turn obstructed the blood supply to distal tissues. Thereafter gangrene developed, but only as a secondary change.

That extreme cold is not necessary to produce frostbite was reemphasized by Hamilton.⁷⁴ He told of 8 seamen who were employed on the fore-castle of a ship in northern waters one early spring afternoon and on the following morning reported with varying degrees of disability as a result of frostbitten fingers. All became wet from an occasional spray coming over the fore-castle. As the amount of disability paralleled the duration of exposure without gloves, the author concluded that the wearing of gloves be strictly enforced at all times.

Raynaud's Disease—The capillary blood pressure of 11 patients with Raynaud's disease and scleroderma was studied by Eichna.⁷⁵ Determinations were made before and after sympathectomy. Pressures were measured in the nail folds of the fingers by the direct microinjection method. Measurements were obtained during vasospastic circulatory arrest and also when the blood flow in the capillaries remained visibly unaltered from the normal. During vasospastic circulatory arrest induced in the fingers by cold, the digital capillary blood pressure varied between 70 and 125 mm of mercury (average, 97 mm of mercury). The digital capillary blood pressure rose slowly in response to induced increases in venous pressure but fell promptly when this pressure was suddenly lowered. Cessation of blood flow through the capillaries was caused by closure of the proximal vessels. The capillaries, venules and veins remained patent. After a period of vasospastic

circulatory arrest, erythrocytes in clumps or loose aggregations could be identified outside the central capillary blood stream on return of the digital circulation. Eichna believed that this was due either to localized constriction of the capillary or to stickiness of the capillary endothelium. In fingers with intact innervation the average digital capillary blood pressure was as follows: arteriolar limb, 185 mm of mercury, summit, 224 mm, and venous limb, 19 mm. The gradient of fall of pressure in the capillary was small, usually less than 3 mm of mercury. In fingers deprived of sympathetic innervation the average digital capillary blood pressure was higher. In the arteriolar limb it was 278 mm of mercury, at the summit, 252 mm, and in the venous limb, 216 mm. The somewhat greater capillary pressure in the arterial limb suggests release of arteriolar tone. The gradient of pressure in the capillary remained small (6 to 7 mm of mercury).

Mufson⁷⁶ reported his observations in 6 cases of Raynaud's disease in which a psychosomatic disturbance was present. He expressed the opinion that cooling of the skin was the trigger mechanism which rendered complete the partial occlusion of the minute vessels but that the process was sustained by personality and social-economic derangements. For treating patients with this disease he recommended a combination of measures directed first to an improvement in mental hygiene and alleviation of social-economic derangements and secondly to an increase in collateral circulation. Although this appears to be an ideal type of treatment, it is difficult to accomplish. Three of his patients improved under this regimen, but the others continued to have cyclic vasospasm because they failed to adjust to their environment. Although emotional disorders are known to aggravate Raynaud's phenomena, it is our opinion that the removal of any psychosomatic disorder is beneficial but not curative for the majority of the patients.

Craig⁷⁷ also studied the relationship of neuropsychiatric disorders to this syndrome. He measured the digital temperatures of a girl known to have a typical Raynaud syndrome during attacks of panic. This was done under controlled conditions, and when the patient was asked questions intended to create anxiety and tension, a drop in surface temperature was recorded. On one occasion a fall of 9.9 degrees C (17.8 degrees F) was noted.

⁷⁴ Hamilton, J. Frostbite, *J. Roy. Nav. M. Serv.* **24**: 225 (Oct.) 1943.

⁷⁵ Eichna, L. W. Capillary Blood Pressure in Man. Direct Measurements in the Digits of Patients with Raynaud's Disease and Scleroderma Before and After Sympathectomy, *Am. Heart J.* **25**: 812 (June) 1943.

⁷⁶ Mufson, I. The Mechanism and Treatment of Raynaud's Disease. A Psychosomatic Disturbance, *Ann. Int. Med.* **20**: 228 (Feb.) 1944.

⁷⁷ Craig, J. B. The Psychogenesis of Raynaud's Syndrome, *Dis. Nerv. System* **5**: 142 (May) 1944.

Scleroderma—During the past few years considerable evidence has been presented to indicate that scleroderma is not necessarily confined to the skin but may involve other organs. Weiss and his colleagues⁷⁸ studied a number of cases of generalized scleroderma and reported the clinical histories of 9 cases with signs and symptoms of heart disease. In 2 of these cases postmortem examinations were performed. Cardiac failure was not uncommon, and in the latter 2 cases it was caused by myocardial scarring of an unusual type. These pathologic observations, together with the clinical data, indicated that scleroderma heart disease should be considered a definite entity. In addition to the cardiac findings, the roentgenograms showed involvement of the lungs. Dysphagia was common, and esophageal stricture was noted.

McLaughlin⁷⁹ reported a case of diffuse scleroderma following the routine inoculations of a recruit in the armed services. This was confirmed by biopsy and was of further interest because a family history revealed that the patient's father had a similar condition.

Scalenus Anticus Syndrome—Two variations in this syndrome have recently been observed. Brown⁸⁰ reported his observations on a case of scalenus anticus syndrome secondary to a paralysis of the trapezius muscle. It was his opinion that this paralysis had caused sufficient sag of the shoulder girdle to place the scalenus muscle on stretch, with resultant hypertrophy and spasm. The author concluded that other muscular disorders of the shoulder could obscure the diagnosis of this syndrome and consequently it should not be limited to a single diagnostic entity.

Three cases of a vascular disturbance in the upper limb due to compression of the subclavian artery and vein between the clavicle and the thoracic rib were described by Falconer and Weddell⁸¹. The patients had symptoms similar to the scalenus anticus syndrome. In 1 case cervical ribs were demonstrated and the subclavian artery was found to be compressed at two places, i. e., between the scalenus anterior muscle and the apex of the cervical rib and

between the clavicle and the first rib. In a fourth case, in which there were neurologic disturbances only, the subclavian vessels were not compressed, and relief was obtained by section of a fibrous band compressing the eighth cervical and first thoracic nerve roots without division of the scalenus anterior muscle.

The authors were able to demonstrate costoclavicular compression by noting the effect of postural movements of the shoulder girdle on the arterial pulses of the arm. Backward and downward bracing of the shoulders, with or without extension of the head, usually obliterated the pulse. Similar movement was also capable of obliterating the pulse in many normal persons, but in those reported on evidence of compression was demonstrated at operation. Symptoms were noted in only those in whom compression was easily provoked. The symptoms ranged from cold, blue hands with a tendency to chilblains to severe vasospastic attacks, arterial thromboses and even gangrene in the persons with more severe involvement. The authors expressed the belief that persons with mild symptoms will benefit from exercises designed to increase the postural tone in the muscles of the shoulder girdle. For the more severe types operation is required.

Causalgia—The nature of painful vasodilatation in causalgic states was recently discussed by de Takats⁸². His conclusions were drawn from a group of 36 cases in which the phenomena of spreading neuralgia and chronic vasodilatation were exhibited. This peculiar vasomotor disturbance has no accepted name, but in de Takats' opinion it includes Vulpain's *état physiopathique*, Weir Mitchell's causalgia, Sudeck's atrophy, Leriche's post-traumatic painful osteoporosis, the peripheral trophoneurosis and the chronic traumatic edema. Three stages of the syndrome were recognizable after the period of trauma. In the first stage, severe and persistent burning pain, with paroxysmal exacerbations due to jarring, air currents or emotional upsets, was typical. The pain was closely limited to the site of injury. The extremity was warm and dry, and edema was noted. Studies of the blood flow and oscillometric curves indicated increased circulation to the injured parts. The condition might subside or progress to the second stage. The periarticular edema and pain began to spread, and the part was not as warm or as flushed as it was earlier. It often became hard, cyanotic and cold to touch. The blood flow was not as active as in the first stage, but there was

78 Weiss, S., Stead, E. A., Jr., Warren, J. V., and Bailey, O. T. Scleroderma Heart Disease with a Consideration of Certain Other Visceral Manifestations of Scleroderma, *Arch Int Med* **71** 749 (June) 1943.

79 McLaughlin, R. R. M. Diffuse Scleroderma, *U S Nav M Bull* **42** 921 (April) 1944.

80 Brown, M. H. Secondary Scalenus Anticus Syndrome, *U S Nav M Bull* **42** 1164 (May) 1944.

81 Falconer, M. A., and Weddell, G. Costoclavicular Compression of Subclavian Artery and Vein, Relation to Scalenus Anticus Syndrome, *Lancet* **2** 539 (Oct 30) 1943.

82 de Takats, G. Nature of Painful Vasodilatation in Causalgic States, *Arch Neurol & Psychiat* **50** 318 (Sept) 1943.

a greater tendency to vasodilatation than in the uninjured limb. The pain had the character of a spreading neuralgia or hyperalgesia, which often defied segmental distribution. In the last stage the atrophy progressed, involving skin, muscles and bone, with ankylosis. Atrophy of the bone became diffuse and indistinguishable from osteoporosis of other origin. The pain was intractable. It sometimes spread to the root of a limb or even to the trunk. In this stage section of posterior roots or chordotomy has not been reported to give relief. Ablation of the sensory cortex has been suggested.

The author discussed the phenomena of vasodilatation in the extremities and reviewed the existing evidence for the presence of efferent fibers of the posterior roots. He suggested that cholinergic vasodilator fibers are activated in this condition and that the resulting capillary hypertension is sufficient to account for the pain. Treatment in the early stages consists of immobilization and daily injections of 1 per cent solution of procaine hydrochloride into the injured areas. With a spread of the neuralgia, para-vertebral injections are necessary, and for the more severe syndromes a sympathetic ganglionectomy was recommended. The late stage will not yield to such peripheral interruptions and requires intervention by psychiatric, and possibly by surgical, methods.

VENOUS DISORDERS

Mayerson and his colleagues⁸³ measured venous pressures in 50 unselected patients and found the height of the pressure to be the same in the normal and in varicose saphenous veins. These measurements were taken with the subjects in the standing position, and in both types of veins the pressures were only slightly higher than the hydrostatic pressure. In the recumbent position, the antecubital and saphenous pressures of patients with varicose veins were found to be significantly higher than normal. This was believed to be due to an increase in blood volume which enabled the subject to compensate for the effects of gravity while standing but led to overcompensation when the recumbent position was assumed.

A new apparatus for the direct measurement of pressure in large and in small veins was described by Burch and Winsor⁸⁴. It is called

83 Mayerson, H. S., Long, C. H., and Giles, E. J. Venous Pressures in Patients with Varicose Veins, *Surgery* **14** 519 (Oct.) 1943.

84 Burch, G. E., and Winsor, T. Phlebomanometer. New Apparatus for Direct Measurement of Pressure in Large and Small Veins, *J. A. M. A.* **123** 91 (Sept. 11) 1943.

the phlebomanometer, and from its description it appears to be compact and easy to handle. No comment was made concerning its accuracy. Burch and Winsor⁸⁵ also reported their observations on the physiologic effect of ligation of the inferior vena cava in 5 patients. This vessel had been ligated below the level of the renal veins for reasons not disclosed. The venous pressure was markedly increased in the veins of the dorsum of the foot for at least ten months postoperatively. Edema developed immediately after the operation, and in only 1 patient did it subside within the ten month period. The rate of loss of water from the skin of the tip of the right second toe and of the pretibial area was normal at the eighth postoperative day, but no measurements had been taken prior to this time for comparison. The peripheral pulse volumes were decreased. The authors concluded that a satisfactory compensation of the circulation followed this procedure.

Bates⁸⁶ reported a case of thrombophlebitis migrans which developed on the twenty-fifth day of scarlet fever. The veins of both legs, including the right external iliac vein, were involved, and improvement followed the use of anti-scarlatinal serum.

An interesting case of phlebitis with migratory and disseminate lesions was described by Flood and his colleagues⁸⁷. Gangrene of the mammary gland developed as a unique complication. Striking improvement followed the use of dicoumarin (3, 3' methylenebis-[4-hydroxycoumarin]). In an "addendum" to the paper, one of the authors mentioned a case of recurrent thrombophlebitis involving a lower extremity in which gangrene of the intestine occurred following a mesenteric thrombophlebitis.

The postmortem observations in a case of thrombophlebitis migrans was recently reported by Swirsky and Cassano⁸⁸. No information was obtained on the cause of the disease. The patient received adequate heparinization, which afforded dramatic and rapid symptomatic relief but failed to prevent further recurrences and thromboses.

85 Burch, G. E., and Winsor, T. Physiologic Studies on Five Patients Following Ligation of Inferior Vena Cava, *Proc. Soc. Exper. Biol. & Med.* **53** 135 (June) 1943.

86 Bates, J. V. Postscarlatinal Thrombophlebitis Migrans, *Brit. M. J.* **1** 665 (May 29) 1943.

87 Flood, E. P., Redish, M. H., Bociek, S. J., and Shapiro, S. Thrombophlebitis Migrans Disseminata, *New York State J. Med.* **43** 1121 (June 15) 1943.

88 Swirsky, M. Y., and Cassano, C. Thrombophlebitis Migrans, *J. Lab. & Clin. Med.* **28** 1812, 1943.

Rheumatic thrombophlebitis of the left internal jugular vein was discussed by Russek and Abbott⁸⁹. This condition was considered a complication in a patient with inactive rheumatic heart disease. After finding fibrosing Aschoff nodules in the wall of the vessels, the authors concluded that the active rheumatic infection persisted in the vein long after the active infection in the heart had subsided.

In 4 of 40 patients with essential hypertension being treated with potassium thiocyanate, Koffler and Freireich⁹⁰ observed a complicating thrombophlebitis. Few supportive data were presented, but the authors said that the frequency of this complication seemed to be greater than could be explained on pure coincidence and that they therefore accepted the drug as the offending agent.

TREATMENT

Nothing new has been added during the past year to the treatment of peripheral vascular diseases. An excellent review of physical medicine in relation to vascular diseases was recently submitted by Allen and Kvale⁹¹. This includes practically all of the accepted physical agents now used by physicians in this field. The value of this article is greatly enhanced by the frequent comments concerning the personal experiences of the authors.

Warshawsky and Dempsey⁹² evaluated the therapeutic response to the three mechanical devices commonly used in treatment of peripheral vascular diseases. These included suction and pressure, intermittent venous occlusion and the oscillating bed. They found the intermittent venous occlusion machine to be the most valuable. Unfortunately, their results were colored by the selection of patients and the frequent use of all three methods. High percentages of improvement were noted with all methods, the least being with the oscillating bed. The authors believed in using all of the methods in a daily routine. The patients were treated from 7 a. m. to 10 p. m. with short rest periods and time for eating. Their schedule included postural exercises, massage with hydrous wool fat or olive oil, whirlpool baths, suction and pressure, sitz baths and intermittent occlusion. Using the

combined three methods, they obtained improvement in 82.8 per cent of patients with arteriosclerosis obliterans, 88.9 per cent of patients with arteriosclerosis obliterans and diabetes, 75.9 per cent of patients with thromboangitis obliterans, 100 per cent of patients with frostbite and 66.7 per cent of persons with residuals of arterial embolism, also in 1 patient with syphilitic endarteritis, 1 with popliteal aneurysm and 2 with arterial thrombosis secondary to polycythemia vera (the only patients with these diseases in the series). No mention was made of the degree of improvement. We do not subscribe to physical therapy in the massive amounts administered, but combinations of a few agents are probably justifiable.

Gambill and Kamenshine⁹³ described a simple apparatus for administering Bueger's exercises. Unfortunately, the method was not described too clearly. Weights and pulleys helped to elevate and lower the extremities with minimum effort by the patient.

Strong and Wallace⁹⁴ administered testosterone propionate to patients suffering from angina pectoris and peripheral vascular disease. The results in angina appeared more promising than those in peripheral vascular disease. Of the 4 patients with the latter disease, 1 reported fairly marked improvement, 2, one of whom was also receiving pavex treatment, said there was slight improvement, and the fourth did not recognize any improvement. Although this series was too small to be of therapeutic significance, its cases can be added to those already published on this questionable method of treatment.

Lahey⁹⁵ described a simple apparatus to produce intermittent negative pressure in one or both legs. An ordinary vacuum cleaner was attached to a box to which a clockwork contact breaker had been added to break the circuit every five seconds. The author was able to produce a negative pressure in the box sufficient to raise a column of water 34 cm. He reported his results in 3 cases. Insufficient data cast doubt on the efficacy of this machine, and at best it can be considered only a simple rendition of the more refined pavex boot.

89 Russek, H. I., and Abbott, G. A. Rheumatic Thrombophlebitis, *Am Heart J* **26** 542 (Oct) 1943.

90 Koffler, A., and Freireich, A. W. Thrombophlebitis, *Am J M Sc* **207** 374 (March) 1944.

91 Allen, E. V., and Kvale, W. F. Physical Medicine in Vascular Diseases, *M Clin North America* **27** 951 (July) 1943.

92 Warshawsky, H., and Dempsey, M. W. Physical Therapy of Peripheral Vascular Disease, *Arch Phys Therapy* **24** 487 (Aug) 1943.

93 Gambill, I. M., and Kamenshine, A. Apparatus for Bueger's Exercises, *M Bull Vet Admin* **20** 173 (Oct) 1943.

94 Strong, G. F., and Wallace, A. W. Treatment of Angina Pectoris and Peripheral Vascular Disease with Sex Hormones, *Canad M A J* **50** 30 (Jan) 1944.

95 Lahey, E. O. Pulsator Vacuum Box for Treatment of Peripheral Vascular Disease, *Lancet* **2** 767 (Dec 18) 1943.

Book Reviews

Health and Hygiene A Comprehensive Study of Disease Prevention and Health Promotion By Lloyd Ackerman Price, \$5.00 Pp 895 Lancaster, Pa., The Jacques Cattell Press, 1943

This book is one of the best for the layman. The author, urged on by the belief that no field of study and instruction has greater potentialities for promotion of the welfare of the individual and society than hygiene has, has emphasized those aspects which concern the average normal person and which he can to some extent influence. Ackerman feels that instruction in hygiene in college is best given during the last two years of the regular course or during the first years of professional education, when the student is best prepared to realize its greatest benefits. The text is therefore meant for a more mature reader than most such works.

The book starts with a discussion of the hygienic concept and reveals the nature, magnitude and objectives of hygiene. This section is followed by a survey of the mortality and morbidity experience of the United States in recent years and a discussion of the prevalence of physical defects and mental disorders. These discussions are well developed and should be easily understood by an adult layman. The evolution of concepts of health is developed from the historical standpoint, leading to the modern experimental approach and methods of evaluation. The reader is then introduced to parasitism and hypersensitiveness, hygiene of the mouth, nutrition, emotions and the intellect, mating and finally exogenous poisons, physical agents and their relations to disease. It is noteworthy that of the 863 pages of text 167 are given to hygiene of the emotions and the intellect and 95 to the hygiene of mating.

The subject is covered in a comprehensive, readable fashion which gives the reader a good grasp of the entire subject.

A Visit to Le Puy-en-Velay By Harvey Cushing, M.D. Price, \$8.00 Pp xiv + 40, with 31 illustrations. Cleveland: The Rowfant Club, 1944.

This recent publication of the Rowfant Club presents a side of Dr. Cushing which all who knew him will appreciate. The volume is a small one, beautifully printed, made from a diary that he kept in 1900, when he was 31 years old and when he traveled abroad by way of a vacation after he had completed his surgical residency at the Johns Hopkins Hospital.

The diary makes pleasant reading. Even more attractive are the illustrations—mainly sketches with a few water colors—which he drew or painted, perhaps to make his diary more vivid or perhaps for his own entertainment.

Too often, the inconsequential—many times the most charming—characteristics of leaders are lost because they are expressed so inadequately in biographies. This bit of Cushing, composed by himself, gives an intimate

glimpse of his companionableness, his artistry, his alertness in observation, his humor and his ability to express himself originally in any medium at hand. The Rowfant Club deserves hearty congratulations for making this unique contribution to medical history.

American Medical Practice in the Perspectives of a Century By Bernhard J. Stern Price, \$1.50 Pp 156 New York: The Commonwealth Fund, 1945.

The New York Academy of Medicine and the Commonwealth Fund, either alone or in combination, are likely to do things well. This book is worthy of both sponsors.

The monograph is well written and gives an amiable account of recent medical history as it has influenced or has been influenced by economic changes, industry, education, urbanization and American life in general. The conclusion is sound. The chief problem of medical practice that agitates the public today is providing for every one a high quality of curative and preventive medical service.

The author, a doctor of philosophy and sociologist, says that the future prestige of the medical profession and the future contribution of medicine to scientific and social progress are closely related to the solution of this problem. He does not give the answer.

Medical Uses of Soap Edited by Dr. Morris Fishbein Price, \$3.00 Pp 182, with 41 illustrations. Philadelphia: J. B. Lippincott Company, 1945.

The statement on the jacket of this book, "Many scattered articles have appeared on specific medical uses of soap, but never before has a reference written by leading authorities so adequately covered this field," summarizes the contents and purpose. Chemistry, process of manufacture, effects on skin and hair, soaps suitable for industrial workers, soaps for shaving and the medical uses of soap are all discussed by experts. The book should be valuable to dermatologists, industrial physicians and others.

An Outline of Tropical Medicine By Otto Saphir Pp 86 Chicago: The Michael Reese Research Foundation, 1944.

Several books of varying size and importance have been published recently, all dealing with tropical medicine. The author of this one terms it neither a textbook nor a handbook but rather an extended vocabulary of the language with which those who practice medicine in the tropics must be familiar.

He writes clearly and has managed to compress a large stock of information within a few pages. The book fits into one's pocket nicely. It will be useful to many readers. It deserves a cordial reception.

El síndrome de Morgagni By Carlos A Campos
Pp 150, with 12 illustrations Buenos Aires, Argentina Iglesias y Matera, 1943

Dr Campos presents a complete discussion of Morgagni's syndrome in this work. The syndrome is described as occurring most frequently in women between the third and sixth decades of life. Cardinal symptoms are a symmetric hyperostosis of the internal table of the frontal bone with a varying neurologic or neuropsychiatric picture. Concomitant obesity is present in about one half of the cases.

The history of the syndrome is reviewed, and a report on 12 cases is included. All of the patients described were women between 30 and 80 years of age, the majority were in the menopause. Eight had arterial hypertension, and 11 had obesity of the rhizomelic type. All had endocranial hyperostosis, localized in the ascending or vertical part of the frontal bone. This symptom, Dr Campos believes, is fundamental and must be present for diagnosis. He classifies hyperostosis into (1) internal frontal hyperostosis, the most common and characteristic type, (2) nebula frontalis, (3) diffuse hyperostosis of the calvaria, and (4) frontoparietal hyperostosis.

A complete clinical study of the syndrome is presented, and Dr Campos believes future studies and theories must keep the following points in mind: (1) Morgagni's syndrome is characterized by a familial tendency, (2) it is almost completely limited to women, the ratio of women to men being 22 to 1, (3) there is pleomorphism between this syndrome and constitutional obesity, (4) the syndrome is vinctuated to acromegaly and other pictures of anterior hypophyseal hyperfunction, (5) it indicates disposition to nervous and mental diseases. Dr Campos encourages physicians to consider Morgagni's syndrome a "heredopathologic syndrome."

The book fulfils its purpose, the presentation of Morgagni's syndrome. Because of the rarity of the disorder, the work is of limited value to the average internist, but it may be of considerable service to those who have a special interest in this type of disease.

Atlas of the Blood in Children By Kenneth D Blackfan and Louis K Diamond Price, \$12.00
Pp 320, with 70 plates New York The Commonwealth Fund, 1944

By tradition the word atlas signifies a book of maps. This particular one is an excellent book of maps revealing how that territory which includes diseases of the blood in children can best be explored.

The contents are arranged ingeniously. About half is devoted to a short monograph describing how blood cells originate, how they look and what happens to them when they become abnormal, and about half is comprised of excellent colored illustrations. The text is not entirely orthodox, for the authors are teachers and have enlivened their style by using words which are known to be popular with students. The various kinds of blood dyscrasias not only are described readably but are illustrated with good diagrams and case records.

The colored plates are works of fine artistry. Each plate has an accompanying diagram, so that any reader can easily find on the plate exactly what he is intended to see. There are enough plates to illustrate almost every type of blood smear.

Diseases of the blood in children are so comparable to diseases of the blood in adults as to make the volume useful to any clinician. The book deserves high praise. Students, practicing physicians and clinical laboratory workers will wish to have it at hand. A copy of it should be found in every hospital and medical school library.

Textbook of Medical Treatment By various authors Price, \$8.00 Pp 1218, with 26 figures and 4 tables Baltimore Williams & Wilkins Company, 1944

This book is an excellent conservative statement of modern treatment in internal medicine. It is interesting to compare British and American practice and to find almost complete correspondence, certainly as to fundamentals. Two minor criticisms may be made. First, some prescriptions are given in metric units and others in apothecaries' units; second, some space is perhaps used to little advantage in brief discussions of treatment of rare or relatively unimportant conditions.

News and Comment

Hermann M Biggs Memorial Lecture—The Hermann M Biggs Memorial Lecture will be delivered by F C Bishopp, Ph D, assistant chief in charge of research, Bureau of Entomology and Plant Quarantine, United States Department of Agriculture, in Hosack Hall, New York Academy of Medicine, on Thursday, April 5, at 8:30 p m. The subject will be "The Medical and Public Health Importance of the Insecticide DDT." The lecture will be given under the auspices of the Committee on Public Health Relations and will be open to the public.

New York Institute of Clinical Oral Pathology—The New York Institute of Clinical Oral Pathology will hold its one hundredth monthly conference at the New York Academy of Medicine on Monday evening, April 30. The subject of the meeting will be "A Survey of the Antibiotic Problem." This will be discussed by members of the medical and dental professions both from the theoretic and from the clinical standpoint. Members of the medical, dental, public health and other professional groups are cordially invited. For further information communications should be addressed to the executive secretary, 101 East Seventy-Ninth Street, New York 21.

SPOROTRICHOSIS IN NEW YORK STATE REPORT OF TWO NEW CASES AND TABULATED DISCUSSION OF TWENTY SIX PREVIOUS ONES

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The sparsity of published clinical reports of sporotrichosis in the state of New York suggests its relatively low incidence. On the other hand, the wide distribution of the *Sporotrichum schenckii* fungus in nature and the infrequency with which one encounters case reports on the more abortive or atypical varieties of sporotrichosis suggest that many infections with this fungus may be overlooked.

Sporotrichosis was first recognized by Luik¹ in 1809. Not until 1889 was it carefully described, by Schenck². We have found only 26 instances of proved or presumptive sporotrichosis recorded as seen in the state of New York during the past four decades (table).

In addition to the previously published 26 clinical reports of proved or presumptive sporotrichosis, observations on 2 recent proved instances of this disease acquired within the metropolitan area of the city of New York are recorded in the table.

REPORT OF CASES

CASE 1—B M, an apparently healthy 14 year old white boy, had a superficial ulcer near the base of his left middle finger during the third week of December 1943. Two weeks prior to this time he had worked for

a florist in New York. Shortly after the ulcer appeared on the left hand a similar one occurred adjacent to the wrist on the medial aspect of the right hypothenar eminence. Within three weeks subcutaneous nodules in linear distribution became noticeable on his forearm. Within six weeks additional nodules appeared, and the condition gradually extended upward toward the right axilla.

Medication during this six week period was limited to magnesium sulfate compresses, local application of heat and application of sulfathiazole salve and powder to the open ulcers.

The history was nonpertinent except for annual attacks of a cutaneous eruption, which occurred chiefly during the summers between the ninth and the twelfth year of age. The description and history of this cutaneous eruption suggested either a mild form of epidermolysis bullosa or erythema multiforme.

With the exception of diabetes in the father there was no history of familial diseases.

Physical Examination—The patient was seen by us during the sixth week of his present illness. At that time he was in excellent physical condition except for the cutaneous lesions on the upper extremities. Two indolent ulcers, one on each hand, and subcutaneous nodules on the right arm were seen on first inspection. The ulcer which first appeared was located on the dorsum of the left middle finger (fig 1A) and the other near the base of the left hypothenar eminence (fig 1B). Both ulcers were situated on a broader erythematous base. They were superficial, irregular in outline and covered with an adherent, gummatous crust. Although the history indicated that the lesion which first appeared was on the left hand, at the time of the first examination no extension of the process was noted on this extremity. However, on the right arm evidence of a progressive extension of the disease toward the shoulder was immediately apparent. Approximately fifteen subcutaneous nodules could be counted, extending in a more or less straight or slightly serpentine line up the lower third of the ulnar aspect of the forearm and then across the volar surface and up the anterior region of the upper part of the arm to within 6 cm of the junction of the axillary fold with the arm. These nodules were only slightly tender and became progressively smaller as they approached the shoulder. The nodules on the forearm, about the size of grapes, were fluctuant, and the overlying skin was slightly erythematous and ad-

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The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the War Department or the Navy Department or the Army or Navy at large.

1 Jacobson, H P. *Fungus Diseases*, Springfield, Ill, Charles C Thomas, Publisher, 1932, p 121.

2 Schenck, B R. On Refractory Subcutaneous Abscesses Covered by a Fungus Possibly Related to the Sporotrichia, *Bull Johns Hopkins Hosp* 9:286-290, 1898.

Chronologic Listing of Cases of Clinically Diagnosed Sporotrichosis in the State of New York

Author	Patient's Residence	Year of Onset	Age of Onset	Sex	Probable Source of Infection	Regions Involved	Clinical Type	Adenopathy	Laboratory Findings	Treatment
Sherrill, S., in discussion on Turrell, G. M. Long Island M J 5 184 188, 1911	Brooklyn (?)	Many yr prior to 1909					Lymphangitic		KI	KI
Sherrill, S., in discussion on Turrell, G. M. Long Island M J 5 184 188, 1911	Brooklyn (?)	Many yr prior to 1909					Lymphangitic		KI	KI
Sherrill, S., in discussion on Turrell, G. M. Long Island M J 5 184 188, 1911	Brooklyn (?)	1909			U'reters on dock		Lymphangitic		Fungous elements in biopsy and smears	KI
Bedell, A. J. Tr Am Ophth Soc 13-720, 1912 1911	New York	1910	17	♂	Right upper eyelid, outer palpebral conjunctiva		Lymphangitic		Culture positive biopsy—chronic inflammatory tissue, serologic test for syphilis negative	KI 1 Gm later 2 Gm tid
Turrell, G. H. Long Island M J 5 184 188, 1911	Long Island	1911	12	♂	Right big toe, back of forearm, left calf		Lymphangitic	No inguinal or axillary	Mycelial threads and "oval bodies" from base of ulcer	10 drops KI tid
Turrell, G. H. Long Island M J 5 184 188, 1911	Long Island	1911	Child	♂	Children's home	Right hand, forearm	Lymphangitic			10 drops KI tid
Lapowski, J. Cutan Dis 37-281 282, 1919	New York	1918	Adult	♀		Right foot, right hand temple	Lymphangitic (single nodule with pain)		Serologic tests for syphilis negative	KI
Graham, J. C. Arch Dermat & Syph 19 382 (June) 1920	Louisiana, New York	1920	6	♂	Knife cut	Lower part of leg	Lymphangitic		Culture negative, biopsy inconclusive	KI, roentgen rays
Wise, F. Arch Dermat & Syph 1 263 (Aug) 1921	New York	1921	31	♂	Brass polisher	Right hand, wrist, arm	Lymphangitic		Culture taken, not reported, biopsy taken, not reported	KI
Hoyt, R. E. U S Nav M Bull 15-809 813, 1921	Guantanamo, Cuba, New York	1921	30	♂	Tropics	Thigh, back, arms and legs	Disseminated subcutaneous with 2 recurrences	No adenopathy	Serologic tests for syphilis negative test for tuberculous positive blood and urine normal, cultures positive	NaI
Fox, H. Arch Dermat & Syph 5 531 533 (April) 1922	Same case as Hoyt's									
Wallhauser, W. J. H. Arch Dermat & Syph 17 863 (June) 1928	New York	1927	7	♂		Upper parts of arms	Lymphangitic		Culture positive	Potassium sulphate, ferric iodide
Levin, O. L., in discussion on Wallhauser	New York	1927					Visceral			Treatment failed, death
Hopkins, J. G., and Benham, R. W. New York State J Med 32 595 601, 1932	Buffalo	1928	6	♂	Barberry bush	Forehead	Lymphangitic		Smear positive culture positive	Roentgen rays, 15 drops KI tid
Hopkins, J. G., and Benham, R. W. New York State J Med 32 595-601, 1932	New York	1929	62	♀	Steel wool	Thighs, right hand forearm	Lymphangitic	No adenopathy	Scratch test negative, cultures positive	KI

Chronologic Listing of Cases of Clinically Diagnosed Sporotrichosis in the State of New York—Continued

Walzer, A Arch Dermat & Syph 2:3 349 350 (Feb) 1931	Brooklyn	1929	26	♀	Housewife	Avillas, chest, arms	Disseminated subcutaneous	Smear negative	"Heavy doses" KI
Mount, L B Arch Dermat & Syph 2:5 528-534 (March) 1932	Albany, N Y	1930	51	♂		Body above waist-line	Epidermal	Serologic tests for syphilis negative, blood and urine normal, culture positive, biopsy—fungous elements in granulomatous tissue	KI
Osborne, E D, in discussion on Bein hauer, L G Pennsylvania M J 39 787 791, 1936	State of New York	Between 1932 and 1936	Adult	♂	Farmer (threshing)	Face	Epidermal	Preauricular nodes	
Osborne, E D, in discussion on Bein hauer, L G Pennsylvania M J 39 787 791, 1936	State of New York	Between 1932 and 1936	Adult	♂	Miller	Face	Epidermal	Preauricular nodes	
Osborne, E D, in discussion on Bein hauer, L G Pennsylvania M J 39 787 791, 1936	State of New York	Between 1932 and 1936	Adult	♂	Miller	Face	Epidermal	Preauricular nodes	
Iewis, G M, and Culmore, J H Ann Int Med 7 991 999, 1933	New York	1932	16	♂	Summer camp	Right hand, arm	Lymphangitic	No adenopathy	Culture positive, smear negative, biopsy—no fungous element in tissue, test for tuberculosis, and serologic tests for syphilis, tular emia, undulant fever negative, blood and blood sugar level normal
Maloney, L R Arch Dermat & Syph 10 1033 1034 (Dec) 1939		1939	18	♂	Porter in contagious disease hospital	Thumb, forearm	Lymphangitic	No adenopathy	Culture negative, serologic test for syphilis negative, biopsy inconclusive
Steeor, J Arch Dermat & Syph 11 1131 1133 (Dec) 1911	New York	1910	63	♂	Insect bite	Finger, right hand, forearm	Lymphangitic	No adenopathy	Serologic tests for syphilis negative, smear negative, culture positive, biopsy—no fungous elements
Traub, E R Arch Dermat & Syph 16 327 328 (Aug) 1942	Long Island	1941	16	♂	Summer camp	Arm, right hand	Lymphangitic	No adenopathy	Culture positive, biopsy inconclusive
Traub, F R Arch Dermat & Syph 16 327 328 (Aug) 1942	Long Isl and	1941					Lymphangitic		
Rullson, R H Arch Dermat & Syph 18 556 557 (Nov) 1943	Bronx, City of New York	1942	68	♂	Gardener	Thumb, right hand, forearm	Lymphangitic		Cultures positive
Combes, F O Arch Dermat & Syph 18 129 130 (July) 1943		1942	31	♂	Last Indian seaman	Arms	Lymphangitic	Epitrochlear	Culture taken, not reported, biopsy inconclusive, blood and urine normal, serologic tests for syphilis and tuberculosis negative
Leiby et al (present case)	Long Island	1944		♂	School boy, worked in florist's shop	Hands, arms	Lymphangitic	Alvllary	Culture and sporotrichin test positive
Gordon, D M to be published	Bronx, City of New York	1944	47	♀	Housewife, worked in garden	Eye lid, preauricular area, forearm	Lymphangitic	Preauricular	Culture and sporotrichin test positive

herent The nodules nearer to the upper part of the arm were pea sized, freely movable beneath the skin and over the underlying tissues, somewhat elastic and covered with apparently normal skin

There was no detectable axillary or cubital adenopathy except for a grape-sized, nontender, firm and freely movable lymph node in the right axilla

Laboratory Data—Under sterile precautions grayish tenacious material was aspirated from a fluctuant nodule on the right forearm This material was used for microscopic and cultural examination

Cultures were reported as showing the presence of *S schenku* by Dr Royal Montgomery of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital The examination of smears from the pus and the bases of the ulcers gave negative results Repeated hematologic examinations and urinalyses throughout the course of the illness gave results which were within normal limits

relief could be noted, but two additional small nodules were discovered on the dorsum of the left hand After this phase rapid healing of the ulcers and involution of the subcutaneous nodules were observed By the sixteenth week of the disease the dose of potassium iodide solution was decreased to 60 drops daily Now only depressed, livid, pigmented scars marked the sites of former ulcers (fig 2A and B) The right axillary lymph node had decreased about a third in size All treatment was discontinued in the nineteenth week of the illness At this time an intracutaneous test with sporotrichin gave strongly positive results for the boy and negative results for the mother (fig 3) The sporotrichin was prepared from a subculture obtained from the initial diagnostic culture taken from the patient³

CASE 2—This case will be outlined only briefly here, as it is being reported elsewhere in detail by Dr D M Gordon, of the department of ophthalmology of Cornell Medical College

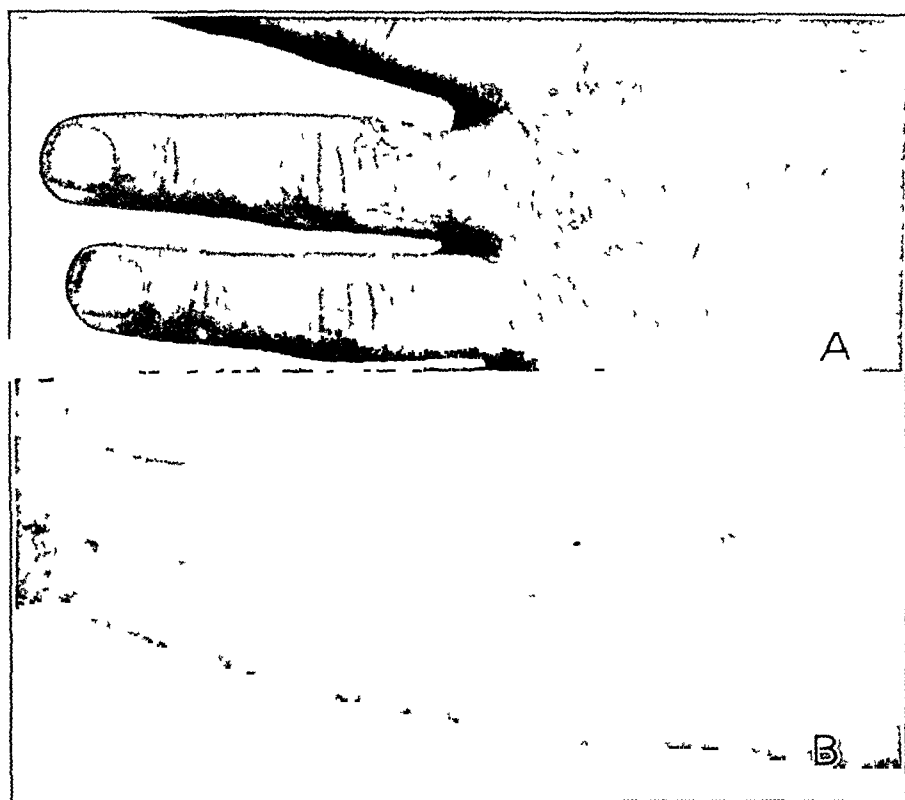


Fig 1—A, sporotrichotic chancre on the left middle finger (six weeks after the onset and before the start of treatment) B, sporotrichotic nodular lesions on the right forearm (six weeks after the onset and before the start of treatment)

Treatment and Course—Treatment was started immediately, with an initial daily dose of 30 drops of saturated solution of potassium iodide given by mouth and a simple zinc oxide lotion applied locally to the ulcerated areas Within forty-eight hours after the iodide medication a distinct flare-up of the lesions, with the appearance of several new nodes, was apparent These happenings were interpreted as a Jarisch-Herxheimer reaction, and medication was continued After subsidence of this first reaction the dose of potassium iodide solution was rapidly increased, and within a week the patient was receiving 120 drops a day This medication was adhered to for ten weeks in spite of transient coryza, herpes on the right side of the upper lip and a slight recrudescence of mild acne

During the first four weeks of this treatment (the seventh to the tenth of the disease) slight symptomatic

Mrs M H, a 47 year old housewife, was first seen in consultation with Dr Gordon in May 1944 There were a bluish red swelling on the left upper eyelid and a pea-sized central crust over a small-bean-sized, fluctuant bulla The cutaneous lesions had then been present about six days A palpable and visible node the size of a small bean was noticed near the external canthus of the left eye and a similar node on the skin of the cheek between the ear and the external canthus, over the malar eminence The skin over these nodes was not freely movable and showed a slightly bluish erythema

The history was pertinent only in that the patient was frequently occupied in gardening About two weeks

3 Dr Donald S Martin, of the department of medicine, Duke University, prepared this sporotrichin for us

before the onset of the lesion of the eyelid she had been cleaning lice from poinsettia plants and recalls wiping her eyelid with her hand

A presumptive diagnosis of sporotrichosis was entertained. This diagnosis was then confirmed by (1) positive culture of *S. schenckii* from pus aspirated from the largest fluctuant lesion⁴, (2) positive cutaneous reaction to intracutaneous injection of sporotrichin derived from the patient in case 1, (3) favorable response to administration of potassium iodide by mouth

COMMENT AND CONCLUSIONS

For purposes of analysis, the 28 cases of clinically diagnosed sporotrichosis (see table) re-

ported as occurring in the state of New York during the last forty-odd years were classified according to clinical types. This classification was not infrequently based on exceedingly cursory clinical information. In four fifths of the cases the disease appeared to be of the localized lymphangitic type. In the remaining cases the cutaneous disseminated forms and systemic types were present.

In the confirmation of the clinical diagnosis some form of bacteriologic or mycologic pro-

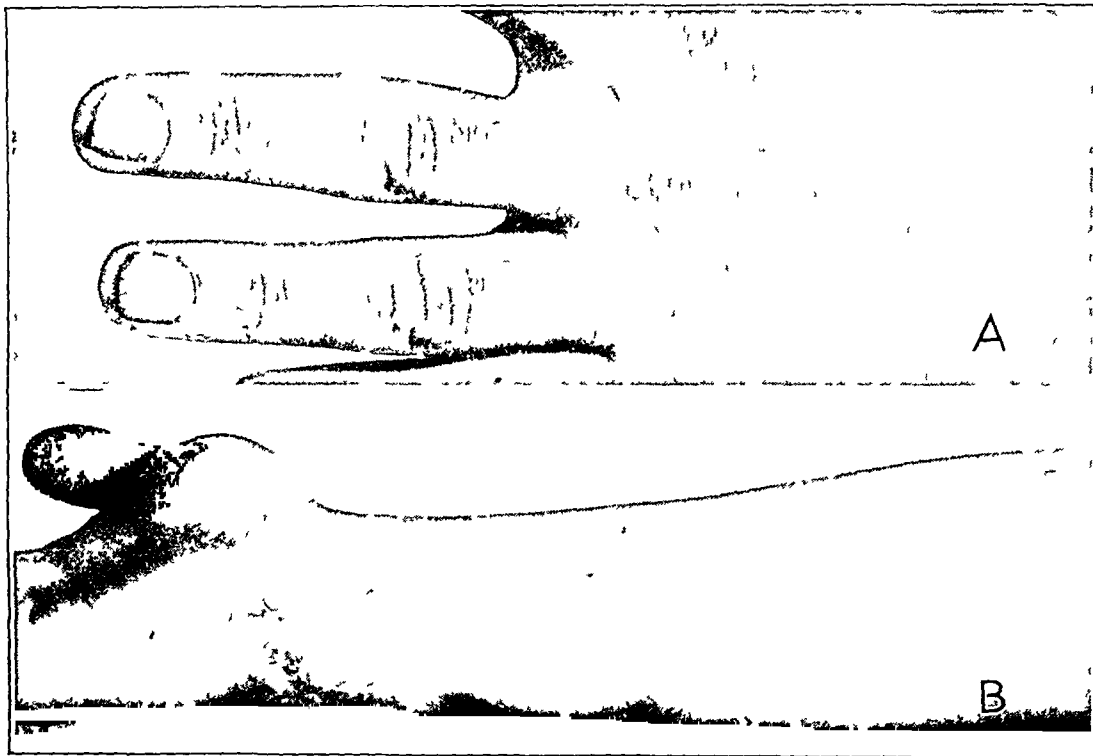


Fig 2—*A*, healed sporotrichotic chancre (same as that shown in figure 1 *A*) on the left middle finger (six weeks after the onset and ten weeks after the start of treatment). *B*, pigmented areas at the sites of healed sporotrichotic nodular lesions (same as those shown in figure 1 *B*) on the right forearm (sixteen weeks after the onset and ten weeks after the start of treatment). Note the remnants of sporotrichotic chancre on the wrist.

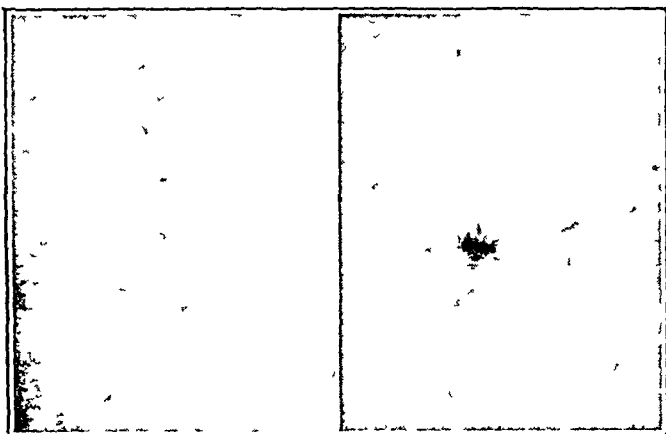


Fig 3—Intracutaneous test with 0.1 cc of sporotrichin: reaction positive on the patient's arm (right) and negative on the arm of the patient's mother (left), who served as a "normal" control.

⁴ Dr. George M. Lewis and Miss Mary Hopper, of the department of dermatology of Cornell University Medical College, prepared and reported on these cultures.

cedure was recorded as attempted in 19 of the cases. Cultures were performed in 16 of these and were reported as giving positive results in 12.

Biopsies were recorded as performed in 10 of the cases. In the tissue examined fungous elements were seen on 2 occasions. Intracutaneous tests with sporotrichin were performed twice and a scratch test once. The scratch test gave negative results. Serologic tests for syphilis were recorded 8 times, tests for tuberculosis 3 times and examinations for tularemia and undulant fever once each.

A majority of the diagnoses were apparently based on linearly distributed, relatively asymptomatic pea-sized to grape-sized subcutaneous nodules on an upper extremity. The initial lesions were indolent, superficial ulcers, and the

subcutaneous nodules tended to be less fluctuant, firmer, more elastic and smaller as one proceeded away from the sporotrichotic chancre. Regional epitrochlear, axillary or inguinal lymphadenopathy was usually not detected in sporotrichosis involving only the extremities.

In the 2 new cases reported here the diagnosis of sporotrichosis was confirmed by (1) positive cultures, (2) positive reactions to sporotrichin tests and (3) response to oral medication with potassium iodide. In 1 case the disease was clinically typical and could scarcely have escaped clinical diagnosis by any physician acquainted with the classic picture. In the second case it

was atypical in localization and by no means absolutely characteristic in appearance.

It is our opinion that such atypical and rudimentary sporotrichosis may often escape diagnosis and that infections with *sporotrichum fungi* may be more common in the state of New York than is indicated by the number of published reports.

The intracutaneous test with sporotrichin is a valuable aid in early diagnosis and should be employed in all cases of suspected sporotrichosis, in addition to the usual cultures on Sabouraud's medium or related mediums.

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HEPATOLENTICULAR DEGENERATION

REPORT OF TWO CASES WITH PREDOMINANTLY HEPATOGENIC SYMPTOMS, ONE ASSOCIATED WITH THE CRUVEILHIER-BAUMGARTEN SYNDROME

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AND

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Wilson¹ in 1912, in an article entitled "Progressive Lenticular Degeneration A Familial Nervous Disease Associated with Cirrhosis of the Liver," first clearly defined the condition now most widely known as hepatolenticular degeneration. His accurate description included and amplified the poorly characterized so-called pseudosclerosis, described by Westphal² and by Strumpell² in the closing years of the last century. Since the publication of Wilson's article, considerably more than 100 cases of this disease have been reported in the literature.

The essential features of the syndrome are cirrhosis of the liver and a bilateral softening and degeneration of the lenticular nuclei. Although not hereditary in the sense of being passed from one generation to the next, the disease has a pronounced familial tendency and frequently affects several children in the same family. As many as five of seven siblings have been known to have the disease. It is a disease of early life and usually occurs in the second or third decade. Its course varies within the wide limits of a few weeks to several decades, the average duration has been estimated to be about four years.³

The chief complaint is commonly a motor difficulty of some sort, and the clinical picture is that of disease of the extrapyramidal motor system. The manifestations vary widely and may include rigidity, dysarthria, tremors, involuntary movements and masking of the facies. In most cases of Wilson's disease there are no signs of involvement of the pyramidal tract, but, if the lesion in the lenticular nucleus becomes extensive enough to extend into the internal capsule, these signs may appear. Disturbances of sensation do not occur.

It is generally true that, although the manifestations due to involvement of the central nervous system may be very severe, there is little or no evidence of hepatic disease. Wilson³ remarked that "this nearly absolute restriction of the clinical phenomena to those of the nervous and mental class is one of the features of the disease." Sweet, Gray and Allen⁴ have shown that reactions to most tests of hepatic function are normal in cases of hepatolenticular degeneration and that it is only with the most delicate tests of this sort that any change can be demonstrated. Walsh,⁵ in reporting 2 cases in which the patients were children, expressed the view that the disease of the liver is in a period of latency and that, with adequate information about the past history, evidence of a transient hepatic disturbance can be discovered.

Hepatolenticular degeneration belongs to the small and select group of diseases which possess a pathognomonic sign. This sign is the pigmented ring occurring at the periphery of the cornea first noted by Kayser² and later by Fleischer² and usually designated by the names of both of these men. The pigment is greenish or brownish and is found in Descemet's membrane. Its chemical structure is still unknown, although spectroscopic studies suggest that it is closely related to urobilin⁶. The ring is frequently visible to the naked eye, but at times it is necessary to look for it with the slit lamp. Although it may be absent in many cases of the disease, the ring alone is generally felt to be adequate evidence on which to establish the diagnosis.

Little or nothing is known about the etiologic factors and the pathogenesis of the syndrome.

From the Division of Medicine, Mayo Clinic

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3 Wilson, S A K. *Neurology*, Baltimore, Williams & Wilkins Company, 1940, vol 2, pp 806-831

4 Sweet, W H, Gray, S J, and Allen, J G. Clinical Detection of Hepatic Disease in Hepatolenticular Degeneration. Report of Nine Cases, *J A M A* **117** 1613-1619 (Nov 8) 1941

5 Walsh, M N. Hepatolenticular Degeneration, *Proc Staff Meet, Mayo Clin* **11** 757-762 (Nov 25) 1936

6 Cusick, P L, in discussion on Walsh,⁵ pp 762-763

REPORT OF CASES

We wish to report 2 cases of Wilson's disease with certain features of interest

CASE 1—An unmarried farmer aged 26 years, came to the Mayo Clinic on Nov 22, 1943, because of swelling of the legs and abdomen. The swelling had begun in the ankles in May 1943 and in the following months had involved successively higher portions of the legs until abdominal swelling had commenced in October. There had been no pain, dyspnea had not been present until the abdominal swelling was far advanced. Other symptoms included only malaise and increased fatigability.

Review of the history by systems revealed that since boyhood the patient had had a fine tremor of the hands and arms, which had been noted especially after exertion. Little or no progression in this tremor had occurred in the past several years. At times there appeared to be an accentuation of it with voluntary movement. For four or five years, he frequently had had cramps in the legs. These had been more severe at night and had been less pronounced since the edema had appeared.

Investigation of the family history revealed that a sister of the patient always had had disproportionately large legs and that she had experienced an episode resembling St. Vitus' dance at the age of 13 years. No further details could be elicited.

Physical examination revealed great enlargement of the abdomen, a fluid wave, upward displacement of the diaphragm and a pronounced pitting edema which extended to the level of the sacrum. There was also a short basal diastolic murmur. Examination of the eyes disclosed well defined Kayser-Fleischer rings.

Neurologic examination revealed very slight abnormalities. There was a rather rapid tremor of moderate amplitude involving the hands, legs and tongue. The tremor did not occur while the patient was at rest, but it was present when the tongue was protruded or the arms outstretched. It persisted with approximately the same intensity during movements of the extremities, such as touching the nose with a finger. There was also a tremor of the closed eyelids. The tendon jerks were moderately increased and seemed slightly more active in the left extremities. The fingers of the left hand could not be wiggled as rapidly as is usually done. The palm-chin reflex (contraction of the facial musculature overlying the chin when the palm is stroked) was present bilaterally to a slight degree. Otherwise, the neurologic examination disclosed no abnormality.

The urine was normal. The concentration of hemoglobin was 13.5 Gm per hundred cubic centimeters of blood. The erythrocytes numbered 4,220,000 and the leukocytes 4,100 per cubic millimeter of blood respectively. Roentgenoscopy disclosed varices of the distal half of the esophagus. The value for the blood urea was 34 mg per hundred cubic centimeters. The value for the cholesterol was 208 mg and for cholesterol esters 124 mg, per hundred cubic centimeters of plasma. The serum protein was 6.2 Gm per hundred cubic centimeters, and the albumin-globulin ratio was 1.1:1.0. The prothrombin time (Quick's method) was eighteen seconds, as was also the average normal control. A sulfobromophthalein sodium test revealed grade 1 retention of the dye, on the basis of 1 to 4.

Peritoneoscopy and abdominal paracentesis were performed on Nov 26, 1943. There was an advanced hobnail type of cirrhosis, grade 4, on the basis of 1 to 4, of both lobes of the liver.

A high carbohydrate, high protein, low fat diet with vitamin supplements was prescribed, and the patient was

dismissed. It was not felt that the neurologic symptoms were severe enough to warrant any attempt at treatment.

CASE 2—A single, white glass worker, aged 24 years, came to the clinic in January 1939, because of a tremor which had been present for a year. At the onset it had involved only his right hand, but it had become progressively worse and had spread to involve the left hand seven months later. It occurred when the hands were at rest but was intensified by movement. The patient could scarcely feed himself, and his handwriting was almost illegible. For three months, friends had noticed that his expression had tended to become fixed. There were some hesitation in speaking and a considerable slowing of voluntary movement.

Examination revealed a pill-rolling type of tremor in both hands, occurring at rest. The patient's movements were all considerably slowed. The facies was masklike and the speech slow and monotonous. There was no detectable rigidity of muscles, and the gait was not typical of Parkinson's disease. After much deliberation on our part, the condition was classified as extrapyramidal dyskinesia—possibly an atypical parkinsonism. The Kayser-Fleischer rings, if present at the time of this examination, were not noticed. The knee jerks were obtained with reinforcement, but the ankle jerks could not be elicited. There were no other findings of neurologic significance.

In January 1940, the patient returned to the clinic, complaining of dryness of the mouth and throat and blurred vision. At this time he was taking stramonium. The results of examination were essentially the same as they had been at the time he first came to the clinic. A preparation of belladonna alkaloids was substituted for the stramonium, and the patient again was dismissed.

On Oct 29, 1943, the patient came to the clinic for the third time. The chief complaint was a greatly swollen abdomen. The history of the period intervening since his previous visit to the clinic is of considerable interest. In the course of the preceding year, there had been a great improvement in the symptoms of which he had previously complained. The tremor had disappeared, and the speed of movement had increased to a point where he had been able to earn his living by driving a truck in a shipyard. His handwriting had improved greatly.

For more than two years prior to his third visit to the clinic, he had noticed distended veins over the lower part of the thorax and upper part of the abdomen. These had slowly become more prominent.

On September 12 he had been awakened in the night, he had felt nauseated and had vomited a large quantity of blood. The vomiting had continued for two days and had been accompanied with melena. A second episode of hematemesis had occurred two weeks later. Treatment at home had consisted of a series of blood transfusions.

Swelling of the abdomen had first appeared on or about October 1 and had become progressively more severe. He had been in bed until four days before coming to the clinic, since he had been out of bed, severe dependent edema had developed.

Physical examination revealed a very pale young man with a rather expressionless face and slight rigidity of the voluntary muscles. No tremor was noted. There was a definite heavy brownish pigmentation around each cornea, which a consultant in the section on ophthalmology classified as unusually well marked Kayser-Fleischer rings.

Over the lower part of the thorax and upper part of the abdomen there were dilated superficial veins, and about the umbilicus there was a well developed caput

medusae (fig 1) In the region of the xiphoid process, a continuous venous murmur was heard (fig 2) The abdomen was greatly swollen and a fluid wave was easily demonstrated The liver could not be felt, but enlargement of the spleen to the level of the umbilicus was demonstrable by ballottement There was a moderate degree of edema of the scrotum and lower extremities

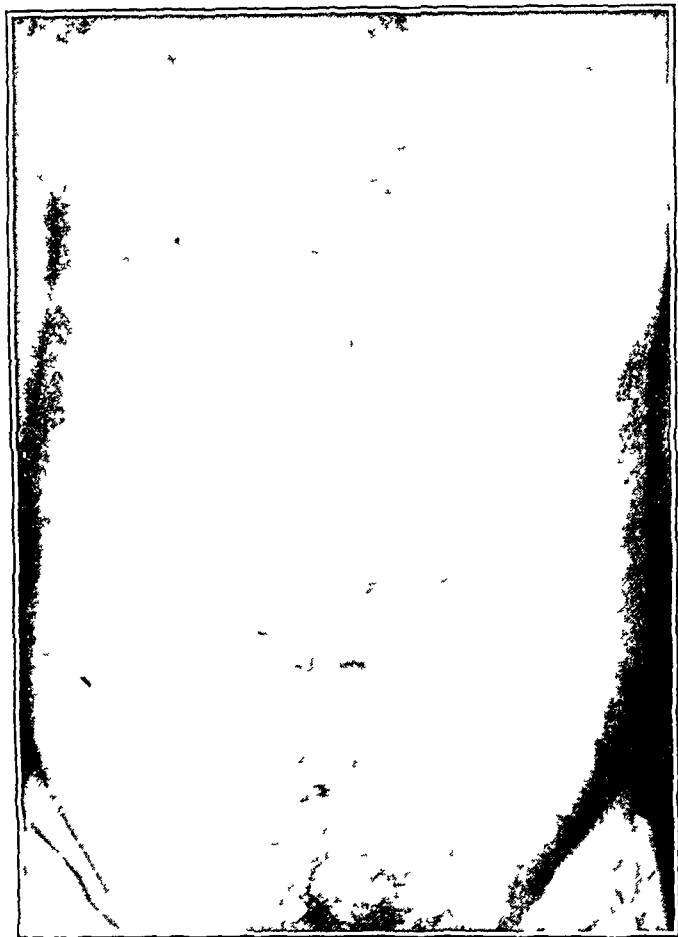


Fig 1 (case 2) —Caput medusae and dilated venous channels on anterior wall of abdomen and thorax (infra-red photograph)

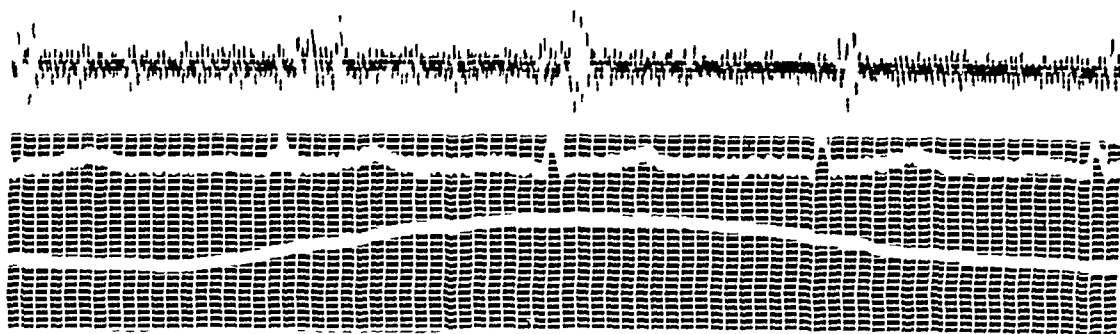


Fig 2 (case 2) —Sound tracing of epigastric murmur in region of xiphoid process (upper tracing) Simultaneous electrocardiographic and respiratory tracings are also shown

Neurologic examination revealed only slight slowness in movement in most muscle groups and that the deep tendon reflexes were moderately to greatly diminished

Laboratory examinations revealed severe anemia and leukopenia The concentration of hemoglobin was 5.3 Gm per hundred cubic centimeters of blood The erythrocytes numbered 2,230,000 and the leukocytes only 1,200 per cubic millimeter of blood, respectively The blood smear showed a hypochromic anemia with increased regeneration The value for the blood sugar was 81 mg and the concentration of serum protein was 5.0 Gm, per hundred cubic centimeters The albumin-globulin ratio was 1.2:1.0. The van den Bergh test re-

vealed that the value for the directly reacting bilirubin was 2.4 mg and the value for the indirectly reacting bilirubin was 0.9 mg per hundred cubic centimeters of serum The value for the cholesterol was 114 mg and for the cholesterol esters 71 mg per hundred cubic centimeters of plasma The value for the fatty acids was 187 mg and for lecithin 132 mg per hundred cubic centimeters of plasma The prothrombin time was twenty-one seconds, as compared with an average normal of eighteen seconds A sulfobromophthalein sodium test of hepatic function revealed retention of the dye, grade 4

In the hospital, the patient was treated with a high carbohydrate, high protein, low fat diet, vitamin supplements and liver extract In addition he was given three transfusions of 500 cc of blood After the transfusions, there was a great improvement in the ascites and edema, with a loss of 28 pounds (12.7 Kg) during his stay in the hospital of ten days In spite of this great improvement there was little objective change in the laboratory findings The value for the serum protein rose only to 5.58 Gm per hundred cubic centimeters, the albumin-globulin ratio was 1.0:1.06, and the value for the hemoglobin increased only a little more than 1 Gm per hundred cubic centimeters of blood, that is, to 6.5 Gm

At the conclusion of his stay in the hospital, he was dismissed with the advice to continue the diet and the use of the vitamin supplements, liver extract and a preparation of iron No treatment was necessary for the mild neurologic signs which still were present

COMMENT

These cases are interesting in that they constitute examples of the rare type of hepatolenticular degeneration in which the hepatic lesion is symptomatically more prominent than the neurologic one Usually, the clinical picture is one of a severe and progressive disorder of movement, and evidence of hepatic involvement is difficult to find The second case is remarkable not only from this standpoint but because of at least two other very unusual features

In the first place, when the patient came to the clinic the first and the second time there was evidence of advanced disease in the basal nuclei, and the usual palliative treatment was instituted In a period of a little less than three years between his second and third visits to the clinic, the symptoms had largely disappeared The patient, although once incapacitated by the tremor and slowness of movement had so improved that he was able to work as a truck driver in a shipyard until forced to go to bed because

of loss of blood. Although the fluctuating character of the neurologic symptoms has been mentioned by Wilson, the progressive nature is usually stressed. Certainly, such noticeable improvement in neurologic symptoms as this patient displayed is rarely observed.

The second outstanding feature of particular interest in this case is the occurrence of another well known but rare syndrome called the "Cruveilhier-Baumgarten syndrome." This term has been applied to a clinical picture of portal hypertension with evidence of excessive umbilical collateral circulation in the form of a loud abdominal murmur or thrill. An enlarged spleen is almost always present. The two physicians after whom this syndrome is named each reported a case, Cruveilhier⁷ in 1852 and Baumgarten⁸ in 1908. At necropsy, in both cases, the umbilical vein was found to be widely patent, the liver was small and atrophic but not cirrhotic, and the spleen was enlarged. It was suggested in their reports that a congenital patency of the umbilical vein was of primary etiologic significance and that the atrophy of the liver was secondary to the shunting of the portal blood away from the liver through this vein.

Since the time of these early reports, a number of similar cases have been recorded, all with evidence of portal hypertension and a well developed umbilical collateral circulation associated with an abdominal thrill or murmur. It has become apparent that in most instances the primary trouble is a cirrhosis of the liver, Banti's disease or some other cause of portal obstruction. When the pressure in the portal system is increased, any collateral route whereby blood can escape from the portal to the caval venous system may be utilized. One of the most common of these routes is the connection between the coronary vein of the stomach and the intercostal, azygos minor and diaphragmatic veins of the caval circulation, which produces esophageal varices.

A well developed collateral circulation in the umbilical region is less common. The umbilical vein, it will be remembered, carries blood during fetal life from the placenta to the liver. Ordinarily it becomes entirely obliterated a few days

after birth and remains as a fibrous cord which passes from the umbilicus to the left branch of the portal vein and is known as the round ligament of the liver. Small veins which accompany it may connect the left branch of the portal vein with the superficial veins about the umbilicus. In a few cases, because of persistent patency of the umbilical vein or because of the increase in size of the paraumbilical veins, a collateral circulation is well developed in the umbilical region. Anastomosis takes place with the systemic veins on the anterior abdominal wall.

The murmur and thrill which are essential diagnostic features of the Cruveilhier-Baumgarten syndrome may be found at various sites on the abdomen but are most common at the xiphoid cartilage or near the umbilicus. They are of venous origin and probably are produced by the rapid flow of blood from a narrow to a widely dilated venous channel.

In 1942 Armstrong, Adams, Tragerman and Townsend⁹ reviewed the cases of this syndrome to be found in the literature. By adding 3 cases of their own, they were able to bring to 55 the number of cases reported. Since then, at least 1 other case has been reported.¹⁰ So far as we know, our case is the first one in which the essential clinical features of the two rare conditions, hepatolenticular degeneration and the Cruveilhier-Baumgarten syndrome, have been observed.

SUMMARY

In 2 cases of Wilson's hepatolenticular degeneration the symptoms and signs of hepatic disease were predominant. In 1 of these cases, an extraordinary remission in the neurologic symptoms had occurred, and, in addition, the features necessary to classify the disease as an example of the Cruveilhier-Baumgarten syndrome were present.

⁸ Armstrong, E. L., Adams, W. L., Jr., Tragerman, L. J., and Townsend, E. W. The Cruveilhier-Baumgarten Syndrome. Review of the Literature and Report of Two Additional Cases, *Ann Int Med* **16**: 113-151 (Jan) 1942.

⁹ Valk, H. L., and Horne, S. F. Cruveilhier-Baumgarten Syndrome (Splenomegaly, Portal Hypertension and Patent Umbilical Vein). Case Report, *Ann Surg* **116**: 860-863 (Dec) 1942.

⁷ Cited by Armstrong, Adams, Tragerman and Townsend.⁸

EFFICACY OF SOME DRUGS AND BIOLOGIC PREPARATIONS AS THERAPEUTIC AGENTS FOR TULAREMIA

J FREDERICK BELL, PH D,¹ AND OSCAR B KAHN, MD

DETROIT

Rather extensive literature is accumulating on therapy for tularemia. Among the numerous agents used for the treatment of tularemia, several have received special mention. These are (1) serum, (2) sulfonamide compounds, (3) arsenic compounds, (4) ferrous iodide, (5) metaphen and (6) acriflavine.

In brief résumé, the first of these, serum, has had the most extensive trials both clinically and experimentally. Unfortunately the work of Foshay¹ in clinical trials and of Francis and Felton² in experimental trials has led to opposing conclusions. The data which Foshay obtained from treating human beings led him to believe that serum effects a significant reduction in both morbidity and mortality. Francis and Felton, on the other hand, concluded that antitularemic serums prepared from horses, sheep and rabbits as well as from convalescent human beings show no evidence of protective effect in white mice.

Many other clinicians have reported on the use of serum in the treatment of tularemia. Some considered Foshay's serum therapy beneficial, but most of the conclusions were based on few cases and lacked parallel series of controls. Hillman and Morgan³ stated that Foshay's antiserum used in an outbreak of tularemia involving 28 persons was without striking results.

With respect to therapy by means of sulfanilamide and other sulfonamide compounds the reports are also conflicting. Curtis⁴ and May⁵

reported successful cures of tularemia with sulfanilamide. Certain other investigators reported the ineffectiveness of sulfanilamide. Weilbaecher and Moss⁶ used sulfapyridine and sulfamethylthiazole as well as sulfanilamide and considered only sulfamethylthiazole to have therapeutic value. The experience of Johnston⁷ is especially enlightening. He stated that "rapid clinical improvement ensued immediately following its [sulfanilamide] use. During the subsequent rise in fever the drug was purposely withheld in spite of which a prompt drop to normal occurred." Johnston concluded that the value of sulfanilamide is questionable. Smith and Rice⁸ noted the failure of therapy with sulfonamide compounds but conversely noted an improvement coincident with the administration of sulfapyridine. To date few well controlled laboratory experiments dealing with the effect of sulfonamide compounds on tularemia have been reported.

Miller and Bannick,⁹ and G. L. and E. G. Powers¹⁰ used a combination of sulfanilamide and antiserum, but they differed in their conclusions as to its value. The former authors regarded it as ineffective. The Powers stated that "there is probably a synergistic action between the tularemia antiserum and sulfanilamide." In each report the opinion was based on only 1 case.

Neosalphenamine, syrup of ferrous iodide, metaphen, autogenous vaccine and acriflavine

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1 Foshay, L. Tularemia. Summary of Certain Aspects of Disease Including Methods for Early Diagnosis and Results of Serum Treatment in Six Hundred Patients, *Medicine* **19** 1-83 (Feb.) 1940

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3 Hillman, C. C., and Morgan, M. T. Tularemia. Report of a Fulminant Epidemic Transmitted by Deer Fly, *J. A. M. A.* **108** 538-540 (Feb. 13) 1937

4 Curtis, W. L. Sulfanilamide in Treatment of Tularemia, *J. A. M. A.* **113** 294 (July 22) 1939

5 May, L. M. Late Tularemic Septicemia. Recovery Following Administration of Sulfanilamide Compounds, *Ann. Int. Med.* **15** 320-323 (Aug.) 1941

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7 Johnston, J. M. Ulceroglandular and Pulmonary Tularemia Treated with Sulfanilamide, *J. A. M. A.* **115** 1360 (Oct. 19) 1940

8 Smith, W. F., and Rice, J. M. Tularemia, *New York State J. Med.* **41** 686-687 (April 1) 1941

9 Miller, J. M., and Bannick, E. G. Tularemia. Report of Case, *Proc. Staff Meet., Mayo Clin.* **13** 494-496 (Aug. 3) 1938

10 Powers, G. L., and Powers, E. G. Tularemia. Report of Case Treated with Sulfanilamide and Antiserum, *Texas State J. Med.* **35** 350-353 (Sept.) 1939

have been used by various clinicians¹¹ with reportedly satisfactory results

The many contradictory reports with respect to the value of the aforementioned therapeutic agents for the treatment of tularemia can only be confusing to the internist who must treat the disease. Our objective in this experiment was to observe results of treatment of a number of animals with the various agents and to compare these data with the data obtained from similarly infected animals which were untreated. We felt that conclusions could be drawn with greater validity from data thus obtained than from the impressions resulting from the treatment of a few patients.

MATERIALS AND METHODS

Guinea pigs were chosen as the animals on which to conduct early experiments, for tularemia is well known in this species. Furthermore, the animals were easily obtainable at the time, and they were large enough to permit the withdrawal of blood for the determination of the levels of the drugs. It was impossible to obtain stock of uniform size, but in each experiment the animals were distributed among the experimental and the control groups so that they were apparently equivalent.

The Vavenby strain of *Pasteurella tularensis*, obtained from Dr R R Parker, was used throughout. Virulence was maintained by animal passage. No attempt was made to insure constant dosages of the infectious culture material in the various experiments, although, of course, in any one experiment the infecting doses given to experimental and to control animals were the same. In general, the method of measuring the doses was to culture the bacteria on a cystine agar medium for about forty-eight hours, to harvest by suspension in isotonic solution of sodium chloride and to dilute to a density corresponding to the no. 6 tube of the MacFarland nephelometer series. Decimal dilutions of this suspension, usually 0.2 cc, were subsequently used for inoculation, which was usually performed subcutaneously in the right inguinal region. In one experiment (no. 7) a triturate of glycerinated spleen from an infected guinea pig was used for the test dose.

The selection of therapeutic doses of the drugs and the manner of their administration were arbitrary and open to criticism. In general the rationale which formed the basis for each test was as follows. The amounts of the drugs given were made larger in proportion to the weight of the subject than the doses given in clinical trials. The doses were kept below toxic levels, however. The therapeutic agents were given very soon after the infecting organisms had been injected, synchronously with them or, in some cases, even before injection of the bacteria. It was intended that if therapeutic efficacy were manifested by these means more severe tests should be instituted by further administration of the drugs in the later states of infec-

tion. The regimens did not correspond in all cases with the regimens which are most effective for human beings. It is desirable to give penicillin to human beings by the constant intravenous drip method, but technical difficulties precluded the use of this procedure for guinea pigs. In an attempt at compromise, penicillin was given by the intraperitoneal and intramuscular routes so that slow absorption would maintain the level in the blood.

To help the reader visualize the amounts of the drugs used, each dose mentioned in the following data is followed by the equivalent dose for a man of average weight. Since the average weight of the guinea pigs was close to 0.5 Kg and since the average weight of men is about 70 Kg, the actual doses used have been multiplied by 140 to allow comparison with the usual clinical doses.

RESULTS

The results of the experiments are presented in graphic form. The charts show the time of survival of the treated animals compared with the time of survival of the untreated controls. In each chart the period of survival of the animals treated with a drug is to be compared with the period of survival of the controls for the same experiment only, since, though a drug may have been used in more than 1 experiment, the infecting doses varied. In every experiment the deaths were due to tularemia.

It should be noted that the scales of both the abscissas and the ordinates in the different charts vary. Each line on a chart begins at a point representing the number of animals surviving after the first fatalities in the series had been discovered.

It may be stated here that control animals were also given injections of the drugs. In only 1 case did an animal show evidence of toxicity. This was 1 of 2 guinea pigs given acriflavine in amounts equal to the test dose. Symptoms of tetany, much like those of strychnine poisoning, developed in the animal, which died in five days. The other animal remained well. The experimental animals did not evidence symptoms of tetany.

Experiment 1 Sulfanilamide and Sulfadiazine (chart 1 A).—Two hundred milligrams of sulfanilamide in the form of 50 mg tablets was administered orally every half hour after infection, 100 mg was given every twelve hours thereafter. If 0.5 Kg is considered the average weight of guinea pigs and 155 pounds (70 Kg) the average weight of men, this is the equivalent of administering 28 Gm as an initial dose and 14 Gm every twelve hours thereafter to a man.

The same course of treatment, with sulfadiazine used instead of sulfanilamide, was applied to 10 animals.

Ten animals were used as controls. At necropsy no lesions or crystals were found in the kidneys of these animals.

¹¹ Barthelme, F L. Metaphen Intravenously in Treatment of Tularemia, *Illinois M J* 72 317-320 (Oct) 1937. Dickey, F G. Tularemia Diagnostic and Therapeutic Study, *Bull School Med, Univ Maryland* 24 143-150 (Jan) 1940. Elson, L N. Treatment of Tularemia, *New Orleans M & S J* 91 296-299 (Dec) 1938. Loria, F L. Treatment of Tularemia with Acriflavine, *Am J M Sc* 202 803-808 (Dec) 1941.

Experiment 2 Metaphen and Acriflavine (chart 1 *B*)—Eight-tenths cubic centimeter of a 1:100 solution of metaphen was injected intramuscularly into the leg of 10 animals at the time of infection, and 0.4 cc of a 1:100 solution was injected subcutaneously into the right inguinal region forty-eight hours later. This amount of solution is comparable to 168 cc of a 1:100 solution of metaphen injected within forty-eight hours into a man.

One cubic centimeter of a 1:100 solution of acriflavine was injected subcutaneously into the right shoulder of 10 animals at the time of infection, and 0.5 cc was injected forty-eight hours later. This dosage is comparable to 210 cc of a 1:100 solution in forty-eight hours for a man.

Ten animals were used as controls.

Experiment 3 Antitularaemia Serum and Sulfamerazine (chart 2 *A*)—Three cubic centimeters of a hyperimmune equine tularemia serum dehydrated to less than

rate of 5 mg per kilogram of body weight one hour prior to infection. The injections were made in the saphenous vein. The comparable dose of mapharsen for a man would be 350 mg. The usual antisyphilitic dose is 60 mg.

Ten animals were used as controls.

Experiment 5 A Preparation of Arsenic and Bismuth and Penicillin (chart 3 *A*)—Two-tenths cubic centimeter of an aqueous solution of bismuth subgallate and sodium para-aminophenylarsonate¹³ was injected into the muscle of the right hindleg of 7 animals at the time of infection and 0.2 cc into the left hindleg forty-eight hours later. This is the equivalent of 56 cc injected into a man within forty-eight hours.

One thousand units of penicillin was injected intraperitoneally into 7 animals every eight hours until the death of the animals. This dosage is comparable to 420,000 units injected every twenty-four hours into a man.

Seven animals were used as controls.

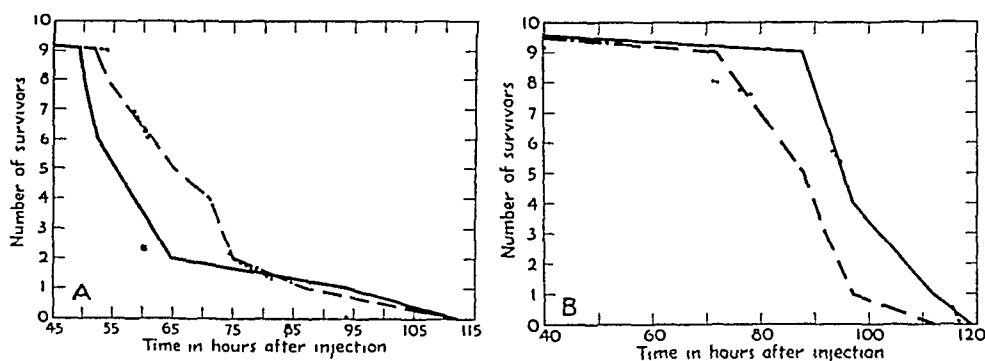


Chart 1—Time of survival of animals given (*A*) sufanilamide (dotted line) and sulfadiazine (dot and dash line) and (*B*) acriflavine (dotted line) and metaphen (dot and dash line). The solid lines are the curves for the control series.

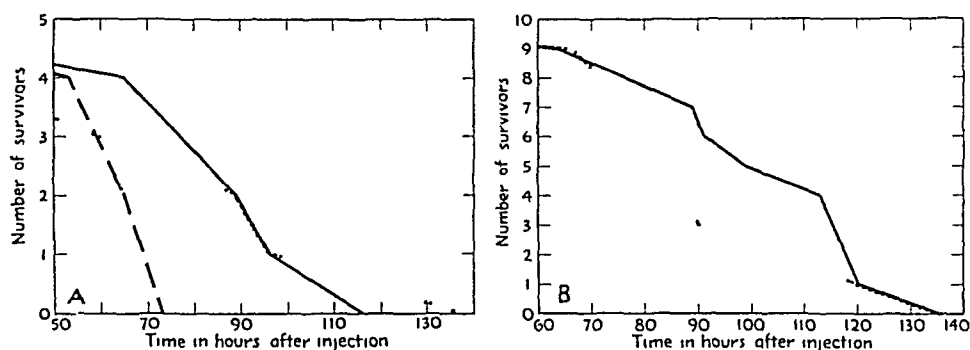


Chart 2—Time of survival of animals given (*A*) serum (dotted line) and sulfamerazine (dot and dash line) and (*B*) mapharsen (dotted line). The solid lines represent the control series.

1 per cent of the residual moisture,¹² representing 6 cc of the original horse serum, was injected intraperitoneally into 5 animals one-half hour prior to infection. The comparable dose for a man is 420 cc of the concentrated serum or 840 cc of horse serum.

Two hundred milligrams of sulfamerazine suspended in a solution of sodium alkyl sulfate (containing 20 per cent of the drug) was given orally to 5 animals one-half hour prior to infection, and the dose was repeated every twelve hours. The comparable dose for a man is 56 Gm every twenty-four hours.

Five animals were used as controls.

Experiment 4 Mapharsen (chart 2 *B*)—The 10 animals in this experiment were given mapharsen at the

¹² The serum used was "Iyovac" (Mulford) anti-tularemia serum.

Experiment 6 Iodobismutol and Stibophen (chart 3 *B*)—Two-tenths cubic centimeters of iodobismutol with saligenin was injected into the muscle of the right hindleg of 7 animals at the time of infection and 0.2 cc into the left hindleg forty-eight hours later. This dosage is comparable to 56 cc injected within forty-eight hours into a man.

Stibophen was injected into 7 animals in the same dosage and at the same site as the iodobismutol.

Seven animals were used as controls.

Experiment 7 Serum and Penicillin (chart 4)—One and five-tenths cubic centimeters of hyperimmune equine serum, dehydrated to less than 1 per cent of the residual moisture¹² (representing 3 cc of serum) was injected intracardially into 7 animals two hours prior to infection.

¹³ The solution used was arseno-bismulak.

tion An equivalent amount for a man would be 210 cc of the concentrated serum

Penicillin was injected into 7 animals The dosage was the same as in experiment 5, but the method of administration was by intramuscular injection rather than intraperitoneally

Seven animals were used as controls

Experiment 7 is the only one in which the results are equivocal It appears that there was a significant increase in the time of survival of the experimental as compared with the control animals Unfortunately in this experiment

The fact that the rate of deaths in the group given penicillin parallels the rate in the group given serum, which other experiments have shown not to survive significantly longer than control animals, indicates to us that penicillin does not appreciably lengthen the period of survival of guinea pigs infected with tularemia

J J Griffiths and C L Larson, of the National Institute of Health, permit me to state that the results of their experiments (unpublished) show no bacteriostatic effect of penicillin on *Pasteurella tularensis* in vitro

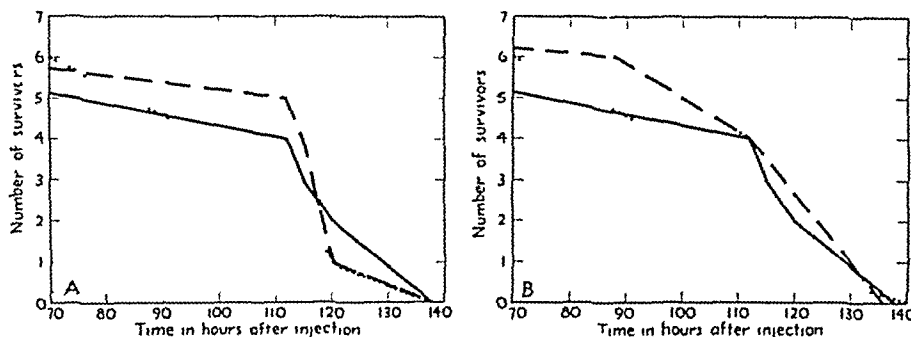


Chart 3—Time of survival of animals given (A) an aqueous solution of bismuth subgallate and sodium para-aminophenylarsonate (dotted line) and penicillin (dot and dash line) and (B) stibophen (dotted line) and iodo-bismutol with saligenin (dot and dash line) The solid lines represent the control series

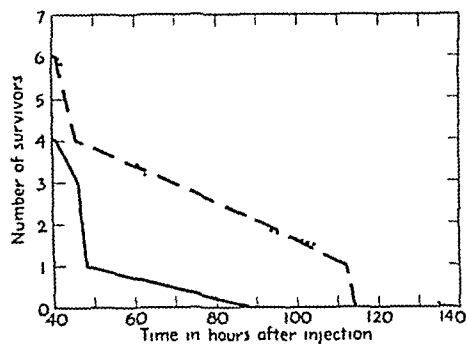


Chart 4—Time of survival of animals given serum (dotted line) and penicillin (dot and dash line) The solid line represents the control series

most of the animals in the control group were not strictly comparable with those in the test groups, for they had not been fed greens previously in comparable amounts Since guinea pigs on a diet deficient in vitamin C are prone to have spontaneous pneumonia, it is possible, if not probable, that the difference in feeding is responsible for the difference in time of survival

SUMMARY

The following therapeutic agents were tested in the treatment of experimental tularemia: sulfanilamide, sulfadiazine, sulfamerazine, acriflavine, metaphen, iodide and bismuth (iodo-bismutol with saligenin), arsenic and bismuth (solution of bismuth subgallate and sodium para-aminophenyl arsonate), trivalent arsenic alone (mapharsen), antimony, (stibophen), penicillin and hyperimmune equine antitularemia serum. All of these substances, penicillin possibly excepted, were used in amounts which proportionately exceeded the doses given human patients. It is our opinion that the results of the therapeutic trials do not demonstrate any advantage in employing these drugs therapeutically.

Dr Lee Foshay, Parke-Davis and Company, Abbott Laboratories, Sharpe and Dohme Company and the staff of the Pharmacology Department of Wayne University College of Medicine provided the experimental animals, serums and drugs used in these experiments

CLINICAL FEATURES OF RELAPSING PLASMODIUM VIVAX MALARIA IN SOLDIERS EVACUATED FROM THE SOUTH PACIFIC AREA

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It is the purpose of this report to describe the clinical features of relapsing *Plasmodium vivax* malaria in soldiers evacuated to the United States from the South Pacific area. Since striking clinical differences may be caused by different strains of the same species of plasmodium and by differences in the host such as race, previous exposure and types of treatment,¹ this report seems desirable in order to acquaint medical officers and civilian physicians with the clinical features of this type of the disease.

The data indicate that the acute attacks are relatively mild, that quinacine hydrochloride is an effective drug both for ridding the blood of the parasites and for control of clinical symptoms and that with the passage of time the rate of recurrence has dropped significantly in this group of soldiers, most of whom were evacuated primarily because of their large number of relapses. The results of laboratory studies of these patients will be presented in separate reports.

SUBJECTS AND METHODS

The subjects of this study were 435 soldiers evacuated from islands in the South Pacific where malaria is endemic.² Although according to their histories many had had infections with both *Plasmodium falciparum* and *Plasmodium vivax*, and although it is recognized that different strains of *P. vivax* may have been responsible for the relapses now reported, never-

theless the soldiers represented a uniform group in the following respects:

- a All but 7 were white
- b All were young adults (the ages ranging from 20 to 40 years for all but 7)
- c Only 8 patients gave a history of proved, and an additional 12 of possible, attacks of malaria prior to exposure in the South Pacific area
- d All had had suppressive treatment in the area where malaria was endemic, mostly with quinacine hydrochloride 0.4 or 0.6 Gm weekly
- e All had had relatively prompt treatment of acute attacks both in areas where the disease was endemic and in areas where it was not endemic
- f All but 4 had had attacks prior to admission to Harmon General Hospital
- g All were observed for a period varying from one to seven months at Harmon General Hospital in an area in which the incidence of indigenous malaria is at present extremely low
- h With the exception of 1 due to a mixed infection with *P. falciparum*, all relapses observed were due solely to *P. vivax*

Patients in the especially created malaria section were quartered in wards of the hospital proper during an initial period of complete medical study and during relapses. At other times they were housed in barracks for convalescent patients where a program of reconditioning was carried out. As soon as symptoms of a relapse developed, thick and thin smears of capillary blood were examined for malarial parasites, and the patient was transferred to a ward for the treatment of patients with acute attacks. Specific treatment³ was never begun until after a smear

From the Eighth Service Command of the Army Service Forces, Harmon General Hospital, Longview, Texas

1 (a) Boyd, M. F. The Infection in the Intermediate Host. Symptomatology, General Considerations, in a Symposium on Human Malaria, Publication 15, American Association for the Advancement of Science, 1941, p. 163. (b) Geiman, Q. M. Medical Progress. Advances in Malaria Research, New England J. Med. **229**: 283 (Aug. 12), 324 (Aug. 19) 1943.

2 Simmons, J. S. Global Malaria, New England J. Med. **229**: 605 (Oct. 14) 1943.

3 (a) The Treatment and Clinical Prophylaxis of Malaria, Circular Letter no. 135, War Department, Office of the Surgeon General, Washington, D. C., Oct. 21, 1942. (b) The Drug Treatment of Malaria, Suppressive and Clinical, Circular Letter no. 153, *ibid.*, Aug. 19, 1943.

had been taken During the first three months of the study, treatment was begun without waiting for the report on the smear if the symptoms were typical, 97 per cent of these smears were reported positive During the last four months, treatment was begun only if the smear was positive and the patient's temperature was 100 F or over

PAST HISTORIES

The length of time spent in zones where malaria was endemic varied from one to three months for 14 per cent of the 435 patients to thirteen to fourteen months for 4 per cent Two hundred and eighty, or 64 per cent, remained four

number of attacks per man varied directly with the duration of the infection It was smallest in the first group, 3.6 attacks per man in five months, and largest in the sixth group, 8.3 attacks in twelve months

Further analysis of the data regarding the entire group of 435 men shows the following Of 98 men in whom the infection was of four to six months' duration, only 14 per cent had had more than 7 attacks, whereas 62 per cent of men whose infection was of ten to twelve months' duration had more than 7 attacks Of 49 men, the known duration of whose infection was thirteen to sixteen months, 37 per cent had had

TABLE 1—Malaria History of Patients Before Admission to Harmon General Hospital

Group	Date of Arrival at Harmon General Hospital	Number of Patients	Average Known Duration of Infection, Mo	Average Number of Attacks per Man	Distribution of Patients According to Number of Attacks					
					1 to 3 Percent ages	4 to 6 Percent ages	7 to 9 Percent ages	10 to 12 Percent ages	13 to 16 Percent ages	Over 16 Percent- ages
	1943									
1	August 16	74	5	3.6	40	50	10			
2	September 29	119*	8	5.4	21	39	32	6	2	
3	October 10	18*	7	4.3	22	33	22	11	6	
4	December 2	106	11	6.2	15	29	33	18	3	2
	1944									
5	January 5 18	33†	8	4.6	36	24	21	9	3	
6	February 15	85	12	8.3	2	21	36	28	8	4

* Includes one patient with no previous attack of malaria

† Includes two patients with no previous attack of malaria

TABLE 2—Relapses of Patients with Malaria at Harmon General Hospital from Admission to March 15, 1944, or to Discharge from Hospital

Group	Date of Arrival at H G H	Average Period of Observation at H G H Mo	Total Number of Patients	Patients with No Attacks		Number of Patients with One or More Attacks				Total Number of Attacks
				Number	Per Cent	1 Attack	2 Attacks	3 Attacks	4 Attacks	
1943										
1	August 16	5.3	74	22	30	17	23	9	3	102
2	September 29	5	119	32	27	39	36	10	2	149
3	October 10	4.5	18	4	22	5	9	0	0	23
4	December 2	3.5	106	33	31	69	4	0	0	77
1944										
5	January 5 18	2	33	1	3	32	0	0	0	32
6	February 15	1	85	47	55	38	0	0	0	33
Totals and averages		3.6	435	139	32	200	72	19	5	421

to six months, 13 per cent remained seven to nine months, and 5 per cent remained ten to twelve months After being evacuated, 30 per cent spent one to three months, 26 per cent four to six months, 24 per cent seven to nine months and 20 per cent ten to twelve months in zones where the disease was not endemic before being admitted to Harmon General Hospital During the period in these areas, suppressive therapy was used not at all or only for variable short periods after arrival, relapses were treated promptly

In table 1 the data regarding the number of attacks have been arranged according to groups of patients as they arrived at Harmon General Hospital As might be expected, the average

10 to 12 attacks, 12 per cent had had 13 to 16, and 4 per cent (2 men) had had over 16 attacks Four men had no attacks prior to admission to Harmon General Hospital

MALARIAL ATTACKS AT HARMON GENERAL HOSPITAL

The number of malarial attacks at Harmon General Hospital is shown in table 2 During the periods of observation indicated for the respective groups a total of 421 clinical attacks occurred in 295, or 68 per cent of the total of 435 patients Two hundred patients had a single attack, 72 had 2 attacks, 19 had 3 attacks, and 5 had 4 attacks Of the 139 patients with no attacks, 47 had been observed for only one

month at the time of the writing of this report. The high incidence of patients with attacks in group 5 (32 of 33) is explained by the fact that most of these patients were admitted to the malaria section because of a malarial relapse after admission to the hospital for some other cause.

Prodromal Symptoms—In 180 (73 per cent) of 245 attacks, there were definite prodromal symptoms before the onset of a chill, well defined chilly feeling or high fever. Headache, backache, weakness and generalized aches were the most common complaints. A few patients complained of nausea or abdominal discomfort and a few of aching testicles. Although in some instances prodromal symptoms were mild or vague and described with difficulty, it was found that the majority of patients could predict an impending attack with accuracy.

Clinical Manifestations of the Acute Attacks—Adequate records were available for analysis of the clinical manifestations in 355 of the total of 421 attacks. The data are summarized in table 3.

TABLE 3—*Clinical Manifestations in 355 Attacks of Malaria*

Symptoms	Number	Per Cent
Chill	281	80
Chilly feeling	30	8
No chill or chilly feeling	43	12
Headache	341	96
Backache	313	88
Generalized aches	311	88
Malaise, weakness	344	97
Nausea	108	59
Vomiting	127	36
Cerebral symptoms	30	8
Tinnitus	92	26
Abdominal pain, right side	112	32
Abdominal pain, left side	149	42
Abdominal pain, none	188	53
Abdominal tenderness, right side	40	11
Abdominal tenderness, left side	89	25
Abdominal tenderness, none	266	75
Spleen palpated	80	23
Liver palpated	19	11*
Herpes labialis	94	27

* Records available for only 173 attacks.

In 80 per cent of the attacks there was a chill, and in only 12 per cent was there neither chill nor chilly feeling. In almost all the patients in whom a chill occurred, it took place prior to institution of therapy. In a few, however, the diagnosis was made on the basis of symptoms other than a chill, plus the findings of parasites in the smear, therapy was then instituted, but it did not always prevent the occurrence of a chill.

There were complaints of headache and of weakness and malaise in 96 and 97 per cent, respectively. In 88 per cent there were backache and generalized aches. Headache and backache were frequently severe and usually lasted for

several days after the subsidence of the fever and other symptoms. Patients complained of abdominal pain in 47 per cent of the attacks, in 32 per cent this was referred to the right side and in 42 per cent to the left. In almost all instances the pain was described as being in the upper part of the abdomen, and when present bilaterally, as it frequently was, it was usually sharper on the left. One patient, however, complained so bitterly of pain in the right upper quadrant of the abdomen with radiation to the right shoulder that a diagnosis of acute cholecystitis was considered until a smear positive for malaria organisms and subsequent prompt subsidence of symptoms with treatment with quina-craine made malaria alone appear the more likely cause for his symptoms. In 75 per cent of the patients there was no abdominal tenderness, in 11 per cent there was tenderness on the right side and in 25 per cent on the left. Frequently the patient complained that it was made worse by deep breathing. The tenderness on the right side was in the upper quadrant of the abdomen in all but 1 patient, and in him there were no physical findings to suggest appendicitis. There were, however, 2 patients who were tardy in reporting symptoms of acute appendicitis because they thought that malarial relapses were developing. In both patients a rise in the number of neutrophils in the blood aided in the diagnosis. In 2 patients in whom lobar pneumonia developed synchronously with malarial paroxysms, the number of neutrophils was sufficiently elevated to indicate that malaria was not the sole cause of their chills, fever and prostration. In 1 of these, the finding of a positive malarial blood smear within four days after completion of a dosage of 2.8 Gm of quina-craine hydrochloride suggests that the onset of lobar pneumonia precipitated the malarial attack. Both patients were treated with sulfadiazine as well as antimalarial medicaments (one with quina-craine hydrochloride and one with quinine sulfate) with prompt recovery both from pneumonia and from malaria.

Nausea and vomiting occurred in 59 and 36 per cent of the attacks, respectively. Because treatment was instituted promptly, one cannot state how often these symptoms were due to malaria, how often to the quinine or quina-craine given and how often to the combination of disease and medication. In 34 of the 208 patients with nausea, the complaint was made definitely before any medication had been given. In only 3 attacks treated with quina-craine was it necessary to discontinue the drug because of vomiting, all 3 patients gave a past history of vomiting severely even when small doses had been given as suppressive treatment. For the remainder of

the patients who had nausea while being treated with quinine, the drug was continued, 1 Gm of sodium bicarbonate^{3b} and some food being given with each dose. Nausea disappeared either because of increased tolerance for the drug or because the acute febrile phase of the malarial attack had subsided. No record was kept of the incidence of diarrhea, but it was an infrequent complaint.

Herpes labialis occurred 94 times, or in 27 per cent of the attacks. In 1 patient the lesions extended from below the right eyelid to the chin. In 1 patient vesicles were present on the tip of the tongue as well as on the lips. In 2 patients herpes labialis appeared before fever (26 per cent). In some of the patients tinnitus occurred before any medication had been given and in others after quinine or quinine had been administered. Approximately half the patients given quinine complained of tinnitus sometimes after only one or two doses. As with the nausea and vomiting, for many patients it was difficult to decide whether the disease or the medication was responsible for the tinnitus.

Closer questioning of patients in whom tinnitus persisted after subsidence of fever revealed that this symptom was frequently a residual of exposure to gunfire and was aggravated by the malarial attack. Another example of the deleterious effect of malaria on preexisting disease is illustrated by the history of a patient who with his first malarial attack had a recurrence of chronic osteomyelitis of the right radius which had until then been quiescent for fifteen years. Subsequently he had ten flare-ups of pain swelling or actual drainage of pus from the sinus scar in his forearm, the flare-ups occurring in all but two instances in association with malarial recurrences. In 1 patient with chronic nephritis of unknown cause hemoglobinuria developed during the first few days of malarial recurrence. Its prompt subsidence with routine antimalarial treatment lent no support to an initial suspicion that the hemoglobinuria was due to blackwater fever.

Cerebral Symptoms—In contrast to the striking cerebral symptoms reported in what were probably falciparum malarial attacks,⁴ such symptoms were conspicuously infrequent in these relapses of vivax malaria, occurring in only 8 per cent. Extreme drowsiness, dizziness, fainting, momentary disorientation and pronounced change in disposition were occasionally noted. The last-named may have been related to the fever and aches or to disgust at the prospect

of another recurrence. Two patients became unconscious within a half hour after the onset of their chills, in 1 of these the delirium was manifested by hallucinations of return to battle. In both patients, symptoms subsided within two hours. One of these patients had a severe psychoneurosis manifested by recurrent attacks of anxiety while under observation. In the second patient hysterical hemiplegia developed after his discharge from the study, it had no relation to a malarial attack. A third patient experienced disorientation for a few minutes at the height of his fever. All these symptoms were probably manifestations of an acute infection rather than signs of cerebral malaria. A fourth patient had an attack of hysterical hyperventilation on the second day of a malarial recurrence, since the age of 17, he had had many such attacks without malaria. The cerebral symptoms in all these patients were probably conditioned as much by the previous personality of the patients as by the effects of the malarial attack. A fifth patient, who for a month before his attack had manifested peculiar behavior, showed evidence of a full blown psychosis on the second day of treatment with quinine for a mild malarial attack. Although quinine was given for only seven days, his psychotic symptoms persisted for over three months until his discharge to a veterans' hospital with a diagnosis of dementia precox—catatonic type. Another patient, with mental deficiency, became confused on the seventh day of treatment with quinine. The acute symptoms subsided within one day after this medication was stopped. Although no attempt was made to reproduce the symptoms, his record indicated a similar experience at another hospital. This is the only patient whose mental symptoms could be attributed to quinine, and they subsided promptly after cessation of the treatment.⁵

Spleen—The spleen was felt, and then only transiently, in 23 per cent of the acute attacks. Although more frequent palpation than was possible under the conditions of this study might have yielded a higher percentage, it is safe to say that what enlargement took place was not striking clinically. This absence of unusual enlargement may have been related to the prompt institution of therapy during acute attacks both past and present.⁶

5 Bispham, W. N. Toxic Reactions Following the Use of Atabrine in Malaria, *Am J Trop Med* 21:455 (May) 1941.

6 (a) Boyd, ^{1a} p 180. (b) Stratman-Thomas, W. K. The Infection in the Intermediate Host. *Symptomatology, Vivax Malaria*, in Symposium on Human Malaria, Publication 15, American Association for the Advancement of Science, 1941, p 183.

4 Talbot, D. R. New Aspects of Malaria, *J A M A* 123:192 (Sept 25) 1943.

It was noted that the incidence of palpable spleen during relapses varied in different groups of patients. For example, in groups 1 and 3 it was palpable in 8 and 13 per cent of the relapses, as compared with 32 and 40 per cent in groups 4 and 6. In table 4 an attempt has been made to relate this finding to the known duration of infection and to the number of attacks before admission to Harmon General Hospital. The groups have been arranged in ascending order according to the incidence of palpable spleen. As might be expected, the longer the duration of known infection and the greater the number of previous attacks, the higher the incidence of palpable spleen during the acute attack. Other factors, however, may have played a part, and their recognition prevents acceptance of this simple relationship as the complete explanation of the differences between groups. The patients in groups 1, 2, 3 and 5 had received quinine for at

TABLE 4—*Relation of Palpable Spleen During Observed Attack to Previous Malarial History*

Group	Spleen Palpated, per Cent of Attacks	Number of Attacks Before Admission, Average per Man	Duration of Known Infection, Months Average
1	8	3.6	5
3	13	4.3	7
2	22	5.4	8
5	23	4.6	8
4	32	6.2	11
6	40	8.3	12

least part of the treatment in from 88 to 95 per cent of their previous attacks, whereas the patients in groups 4 and 6 received quinine as partial treatment for only 33 and 42 per cent of attacks. Furthermore, most of the patients in groups 4 and 6 were members of the same infantry division and presumably had their exposure to malaria under similar conditions which were perhaps different from the conditions in the other groups, with respect to both the nature and the amount of infection. In the absence of controlled studies, final judgment must be deferred as to the explanation for the observed differences in splenic enlargement.

Fever.—The maximum (oral) temperatures attained are indicated in figure 1, and the prompt subsidence of fever in 313 attacks treated solely with quinacrine hydrochloride is shown in figure 2. In figure 3 are presented examples of the two most typical varieties of temperature curves obtained following the administration of quinacrine. Of two hundred and ninety-two graphic temperature records available for analysis, 139 showed one peak and 153 two peaks. No striking difference was found between these two groups in the incidence of positive smears

on the day after treatment with quinacrine had been started. Seventy-eight per cent of the patients with two peaks and 62 per cent of those with one peak had positive smears on the morning after treatment had been started.

With the treatment outlined in table 5 there was a prompt subsidence of acute symptoms,

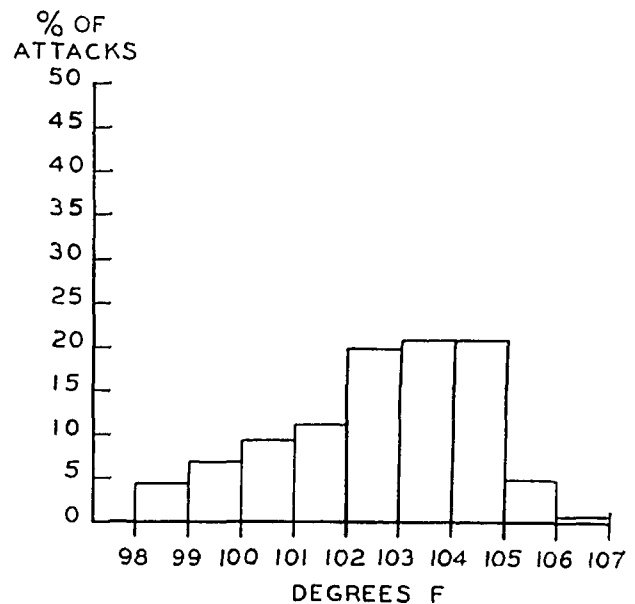


Fig 1—Distribution of maximum oral temperatures in 354 relapses of vivax malaria

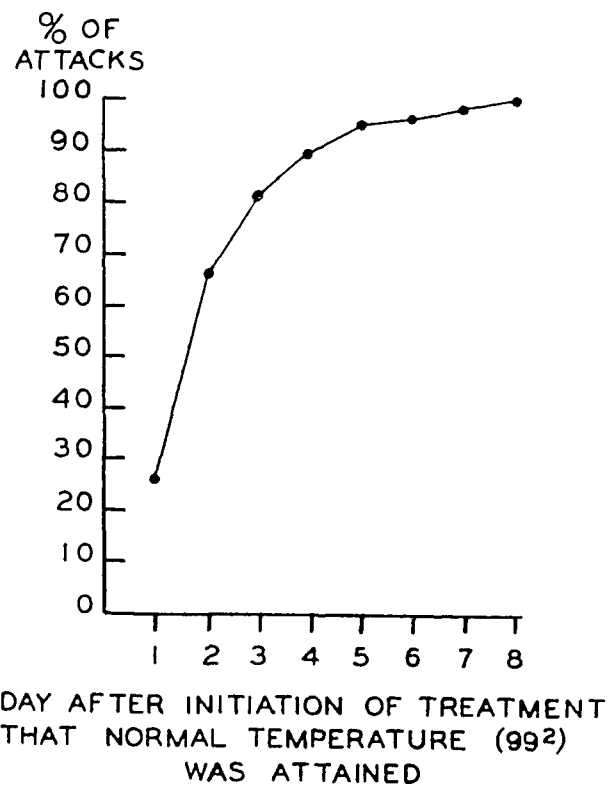


Fig 2—Effect of administration of quinacrine hydrochloride on temperatures in 313 attacks

and the great majority of the patients needed to be persuaded of the desirability of remaining restricted to the ward until therapy was completed. In figure 4 the effect of quinacrine hydrochloride on the incidence of positive malarial smears is presented for 200 unselected patients for each of whom a smear was examined

before treatment was started and every day thereafter for four days. All patients had positive smears before treatment was started. In smears

the second day of treatment this had dropped to 10 per cent, on the third day to 1.5 per cent and on the fourth day to 1 per cent. Thus, after forty-eight to seventy-two hours of treatment there was virtually complete absence of parasites from the peripheral blood. The great efficacy of quinacrine in controlling symptoms and fever is thus a reflection of its effect on parasitemia.

Comment—Several distinctive features of the disease as it is seen in soldiers returning to this country have been noted in the study of this group of patients. Although approximately 30 per cent of the patients who said they knew the causative Plasmodia of their past malarial attacks incriminated both *P. falciparum* and *P. vivax*, all the attacks observed here were due to *P. vivax* with the exception of one, in which both Plasmodia were identified.

The two chief general characteristics noted, namely the great tendency to relapse and the relative mildness of the acute attack under the treatment outlined previously, conform to customary descriptions of vivax malaria.⁷ The relative mildness of the acute attacks was manifested by the infrequency of cerebral manifestations, vomiting and other troublesome symptoms and by the prompt response to therapy. In only 1 patient was the response unsatisfactory to

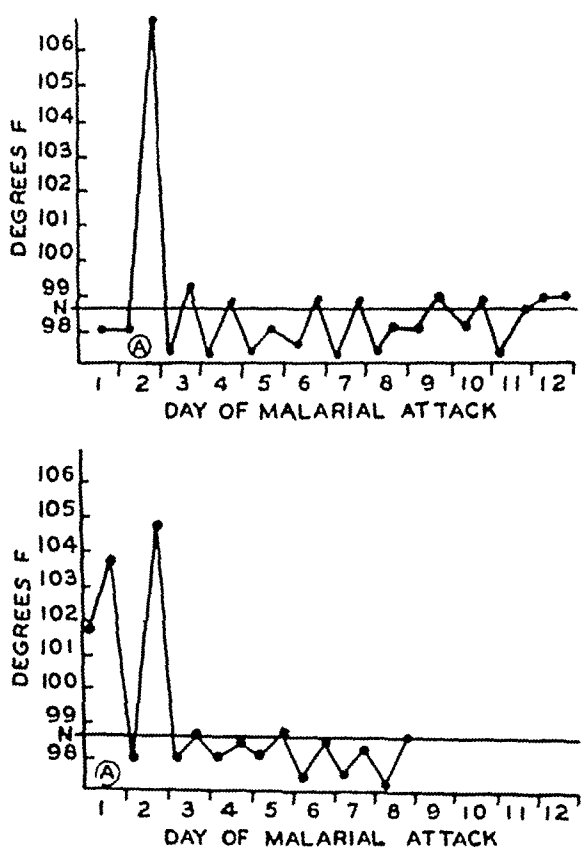


Fig 3—Typical temperature curves with quinacrine hydrochloride therapy. (A) indicates day on which quinacrine hydrochloride was started in dosage shown in table 5.

TABLE 5—Therapy Used in 421 Clinical Attacks *

Number of Attacks	Drug Used	Schedule of Dosage, Gm	Total Dose, Gm
14	Quinine sulfate (3a)	1.0 three times a day for 2 days then 0.64 three times a day for 5 days	16
16	Quinine sulfate	0.64 three times a day for 3 days then	6
	Quinacrine hydrochloride	0.1 three times a day for 5 days	1.5
	Pamaquine naphthoate (3a)	After 2 days' rest then 0.01 three times a day for 5 days	0.15
335†	Quinacrine hydrochloride (3b)	0.2 every 6 hours for 5 doses then 0.1 three times a day for 6 days	2.8

* For 21 attacks various combinations of the three drugs were used. For 35 attacks the details of treatment were not known because patients were absent from the hospital at the time of the attacks.

† In 129 of these attacks the treatment (2.8 Gm of quinacrine hydrochloride) was followed by 0.1 Gm quinacrine hydrochloride daily for a total of 60 days of treatment. In 60 of these, 0.01 Gm of pamaquine naphthoate was given three times a day for 3 days, beginning 1 day after completion of quinacrine hydrochloride (2.8 Gm) and before the daily dose of quinacrine hydrochloride (0.1 Gm) was begun.

examined from eight to twenty-four hours after treatment was begun, that is, after from 0.4 to 1.0 Gm of quinacrine hydrochloride had been ingested, 60 per cent showed malarial parasites. On

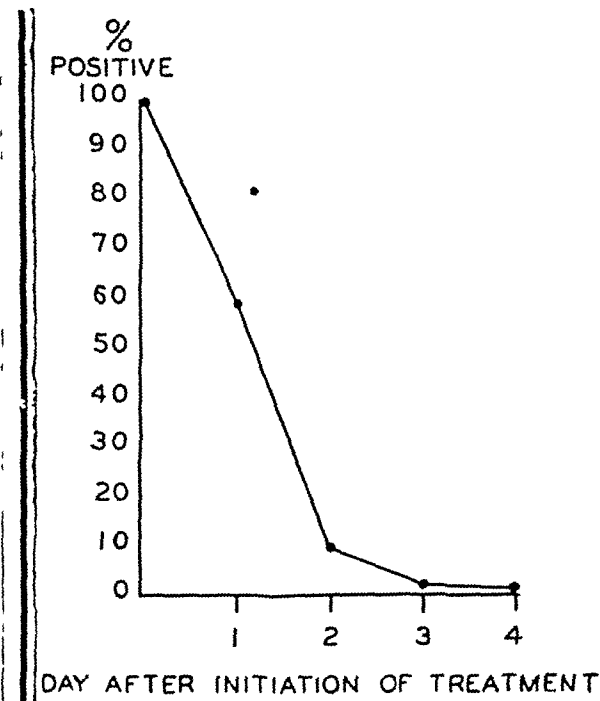


Fig 4—Effect of quinacrine hydrochloride on malaria smears taken daily for five days during 200 attacks. All smears were positive before treatment was started.

quinacrine given orally, quinine sulfate was substituted after four days in which chills and fever continued in spite of the administration of

⁷ Strong, R. P. *Stitt's Diagnosis, Prevention and Treatment of Tropical Disease*, ed 6, Philadelphia, The Blakiston Company, 1943.

quinacrine hydrochloride in the usual dosage. Unfortunately, the amount of quinacrine in the plasma was not determined for this patient. In the beginning of this study, quinine was given orally in preference to quinacrine to 2 patients who became unconscious shortly after the onset of their chills, to several patients in the closed wards of the neuropsychiatric section and to 1 patient convalescing from an appendectomy. At the present time, having observed the great efficacy of quinacrine in the treatment of acute paroxysms of vivax malaria, we are using it routinely with good effect even under unusual conditions such as those outlined. Excellent results have been reported when quinacrine hydrochloride was given parenterally for the treatment of cerebral malaria.⁸

In spite of the good immediate response to the therapy described, the large number of relapses presents a significant problem. First, good medical care for each attack requires ideally that the soldier be hospitalized for a week or ten days. Second, a large number of the patients complained on admission of not feeling up to the usual standard of health between attacks. Evaluation of these symptoms has been difficult. A thorough review by systems when the patients were admitted to the hospital frequently led to exaggeration of symptoms in a group of men such as these, whose chief interest was their return to their homeland rather than rehabilitation for active duty.

At the time of their admission to Harmon General Hospital about a third of the patients complained of weakness, easy fatigability, palpitation or of dyspnea after exertion. Two patients had aortic insufficiency and paroxysmal auricular tachycardia, respectively, but in the remainder of those whose symptoms persisted, no evidence of heart disease could be found through physical examination, exercise tolerance tests, roentgenograms or electrocardiograms. In 287 patients whose charts were available for this analysis, only 7 showed less than 4,000,000 and 72 less than 4,500,000 red blood corpuscles per cubic millimeter of blood at the time of their admission to Harmon General Hospital. Only 3 had less than 130 Gm and 26 less than 140 Gm of hemoglobin per hundred cubic centimeters.

In approximately two thirds of 300 patients the admission weight was 10 pounds (4.5 Kg) or more below their stated usual weight. For 57, or 19 per cent, the apparent weight loss was between 20 pounds (9.1 Kg) and 29 pounds

(13.2 Kg), for 13 (4 per cent) between 30 pounds (13.6 Kg) and 39 pounds (17.7 Kg), and for 3 (1 per cent) more than 40 pounds (18.2 Kg). It is possible, however, that many patients overestimated their usual weights. Approximately one half of 140 patients had ill defined gastrointestinal complaints, chiefly anorexia. In the majority of patients this symptom improved noticeably under the stimulus of the relatively sheltered existence of the convalescent program. It was mirrored in weight gains in an average of three and three-tenths months of from 6 pounds (2.7 Kg) to more than 25 pounds (11.4 Kg) in 120 or 46 per cent of 256 patients for whom records are available.

About two thirds of 135 patients complained of headaches for which, with few exceptions, no organic cause could be found. Likewise, about two thirds of 123 patients complained of nervousness, including insomnia. Fifty-two of 128 patients had complaints referable to the eyes, these consisted of burning, lacrimation, blurring of vision or ocular fatigue. Seventeen of these patients were found to have refractive errors, chiefly of astigmatism, and corrective glasses were provided. Thirty-one of 123 patients had complaints referable to the ears, chiefly loss of auditory acuity or tinnitus. In 12 of these, special examinations did reveal slight impairment of hearing, but it was impossible to decide whether to relate this to malaria, to quinine or to exposure to gunfire. Depending on the thoroughness and persistence of questioning a variable and not inconsiderable number of men complained of backache and pains in muscles and joints. Of 28 men whose backache led to an orthopedic consultation, 15 were found to have adequate cause, such as arthritis, poor posture or a definite history of back strain.

To what extent these residual symptoms could be attributed to malaria, to what extent to other infections suffered in the South Pacific area and to what extent to the physical and mental rigors endured it is difficult to say. Although some of the patients suffered from severe psychoneurosis and could not be expected to surrender their somatic complaints under symptomatic treatment, others, who seemed well adjusted, also complained of easy fatigability. In contrast there was a small minority of patients with a history of multiple attacks of malaria who showed no signs of either emotional or physical disability.

REHABILITATION

Shortly after the first two groups of patients with malaria had been admitted to the hospital, the need for a program of rehabilitation became

⁸ Kirzon, M. I. The Treatment of Malaria in the Zone of Operations, *Am Rev Soviet Med* 1:226 (Feb) 1944.

obvious. As has been mentioned, a majority of the patients had somatic complaints for which no definite organic cause could be found. In those who seemed well adjusted emotionally one could easily believe that the recurrent bouts of feeling "rough" for several days represented subclinical malarial attacks which never developed to the point of parasitemia or a paroxysm. In many, however, the complaints were persistent rather than intermittent and seemed to stem as much from factors such as exposure to severe combat and living conditions in the South Pacific area or previous personality problems as from recurrent malaria. For some patients, malaria was the tangible clutch with which they hoped to avoid further military duty, others, with greater personal insecurity, went further in their speculation about the future and felt that malaria would interfere with their ever being useful citizens again even in civilian life. Since treatment of such symptoms could scarcely succeed in the atmosphere of a customary hospital ward, two barracks originally planned for duty personnel were opened for the malarial patients. Here, under noncommissioned officers picked from their own number, they were organized in groups similar to the ones in which they had served when well. They stood reveille, inspection and retreat, were given the same pass privileges as duty members of the hospital detachment and had graduated physical exercise. Immediately after their admission to the detachment of convalescent malarial patients, they were interviewed as to educational and occupational background, both civil and military, and assigned to duties in and about the hospital. Here they made a positive contribution to the running of the hospital. In addition to the jobs filled in their own organization, they worked as clerks, messengers, typists, dental and laboratory assistants, guards, repair men and ward men. Two men played in the hospital orchestra, 3 on the hospital baseball team, 1 became art editor of the hospital paper and 1 helped as an instructor in the occupational therapy department.

The resumption of the semiduty status at useful and necessary work not only gradually developed physical stamina but restored self confidence and contentment to a degree not possible as long as the men were kept in the usual status of patients. This restoration was particularly evident among the noncommissioned officers, for whom the return to semiduty permitted some resumption of the responsibility and authority which they had earned in service and which while patients they could not enjoy. The opportunity to identify themselves with the functions of the hospital, not solely as patients but also as

contributors to its efficiency, at the same time that they were being reassured that their disease was "burning itself out" helped prepare them for return to more active duty or civilian life.

PROGNOSIS

Of the greatest importance to both the Army and the individual patient is the question of prognosis. In table 6 and figure 5 are presented data which indicate a decreasing rate of relapse.

In table 6 are compared the number of clinical attacks experienced by the group of 72 men during two continuous periods of four and one-half and five and one-half months in areas where malaria was not endemic. They were selected for this analysis because they had all left the area where the disease was endemic on the same day and were under observation here for the same period of time. Following the period of three or six months in the area in which they

TABLE 6—Comparison of Number of Attacks in Areas Where Malaria Was Not Endemic Before and After Admission to Harmon General Hospital

Group	Number of Patients	Time in Area Where Malaria Was Endemic, Mo	Total Attacks in Area Where Malaria Was Not Endemic	
			Before Admission (4½ Mo)	After Admission (5½ Mo)
1	59	6	161	84
2	13	3	32	17
Total	72		193	101
Mean attack per man			2.68	1.40
Probable error of mean			0.105	0.075
Difference between means			1.28 ±	0.129
Mean attacks per man per year			6.99	3.03

contracted malaria, they spent four and one-half months in a South Pacific area where it was not endemic. During this period there were, according to their own accounts, a total of 193 clinical attacks, or an average of 2.7 attacks per man (6.99 per man per year). Following this, they were observed for five and one-half months at Harmon General Hospital. During this period, one month longer than the previous one, they had a total of only 101 clinical attacks, or an average of 1.4 per man (3.03 per man per year). Thus the frequency of attacks decreased by approximately one half during this relatively short period of observation.

In figure 5, data are presented on the rate of relapse after the patients' evacuation from the area where malaria was endemic in each of four convoys. From 74 to 119 men were available for analysis of recurrences during the first month following evacuation and from 54 to 80 men during the last month of observation. The period of direct observation at Harmon General Hos-

pital averaged five and three-tenths, five, three and one-half and one month for the four groups, respectively (table 2). The data for the previous months were obtained from the soldiers' own histories without supporting documents. It is seen that in each group a striking drop has taken place in the percentage of men having malarial attacks. These results confirm the clinical impression gained from observation of the general appearance of the men that the disease is dying out.

The differences between the curves for the four groups (fig 5) point to difficulties that may arise in interpretation of the relative efficacy of different modes of therapy in preventing

in preventing recurrences can be carried out most profitably shortly after the evacuation from the zone where malaria is endemic of large groups of soldiers with similar histories of exposure, who are kept under the same controlled conditions of general care.

Although only 19 per cent of 124 men for whom data are available for twelve months had an attack during the twelfth month after evacuation from the zone where the disease is endemic, few of them could be pronounced cured of their malaria. An analysis of the longest interval that had elapsed between known attacks during the twelve month period reveals that for 5 men (4 per cent) this maximum period without an attack was only one month, for 22 men (18 per cent) only two months and for 45 men (36 per cent) only three months. In 4 men (3 per cent) attacks occurred after seven, eight or nine months of freedom from definite paroxysms. At the twelve month point there were only 9 men (7 per cent) who had been free of clinical attacks for six months or more. It must be emphasized, however, that these figures derived from a group of men evacuated primarily because of relapsing malaria cannot be used for prediction purposes on the original large group of soldiers infected overseas under similar conditions.

SUMMARY AND CONCLUSIONS

The clinical manifestations of 421 attacks of vivax malaria occurring in a group of 435 soldiers evacuated from the South Pacific area have been studied.

The essential clinical features of the disease observed were the pronounced tendency to relapse and the relative mildness of the acute attack.

Quinacrine hydrochloride was found to be an effective agent for prompt control of the clinical symptoms and for eradication of parasites from the blood.

Although most of the soldiers in the study had been evacuated because of the recurrent nature of their disease, evidence is presented to indicate that the rate of relapse is decreasing as time goes on.

A program of rehabilitation was instituted with great benefit to the development of physical stamina and the restoration of self confidence.

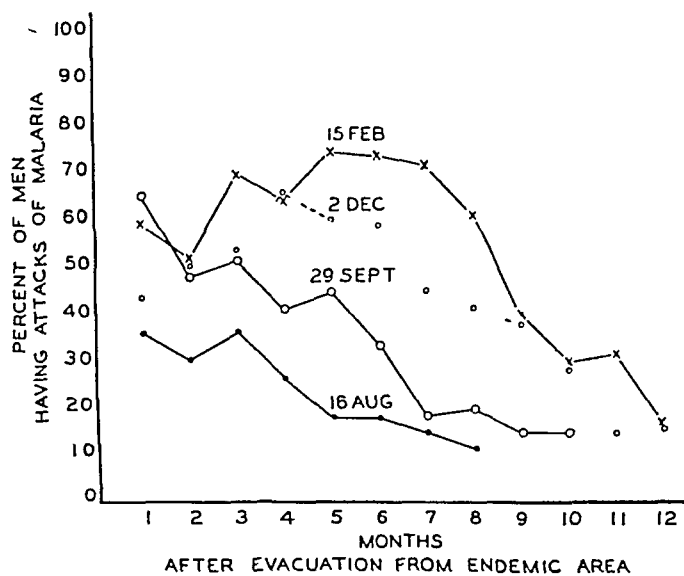


Fig 5—Monthly incidence of relapses following evacuation from area where malaria was endemic. The numbers of men available during each month for which the rate of relapse was calculated were as follows:

Group Arriving on	Months After Evacuation from Area Where Malaria Was Endemic											
	1	2	3	4	5	6	7	8	9	10	11	12
Aug 16	74	74	74	74	73	65	54					
Sept 29	119	119	118	117	117	113	111	106	91	80		
Dec 2	104	104	104	104	104	102	102	102	98	89	81	69
Feb 15	85	85	85	85	85	85	85	85	77	77	77	55

malarial relapses. For example, in the sixth month following evacuation from the area where the disease was endemic, the percentages of men having relapses were 18, 34, 59 and 74, respectively, in the four groups. These variations may depend on differences in the nature or amount of the original infection or infections, the nature and amount of drugs used in treatment or on other factors in care. These considerations suggest that studies of the efficacy of different drugs

ABSORPTION, EXCRETION AND DISTRIBUTION OF SULFAMETHAZINE

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The search for the ideal sulfonamide compound has directed our attention to sulfamethazine, the latest of the sulfonamide compounds. Sulfamethazine (2-sulfamylamido-4, 6-dimethylpyrimidine) is the dimethyl homologue of sulfadiazine. The few reports now in the literature credit it with less toxicity than the sulfonamide drugs now in use. Rose, Martin and Bevan¹ compared the solubility of this compound and its acetyl derivative with that of sulfapyridine, sulfadiazine and sulfathiazole. Sulfamethazine was found to be ten times more soluble in the free and five times more soluble in the acetylated form than sulfadiazine. Gilligan and Plummer² showed it to be the most soluble of all the sulfonamide compounds in the varying range of urinary p_H in both its free and its acetylated form. Clinical studies have been made by Macartney and his associates³ and others⁴ on the use of the drug in the treatment of pneumonia in adults and by Jennings and Patterson⁵ on its use for children. These writers report that its therapeutic effects are as good as those of the other sulfonamide drugs and its toxic effects fewer.

The following studies, made at Cook County Hospital during the season of 1943-1944, present

From Cook County Hospital and Loyola University School of Medicine

1 Rose, F L, Martin, A R, and Bevan, H G L. Sulphamethazine (2-4'-Aminobenzenesulphonylamino-4-6-dimethylpyrimidine). New Heterocyclic Derivative of Sulfamylamide, *J Pharmacol & Exper Therap* **77** 127 (Feb) 1943

2 Gilligan, D R, and Plummer, N. Comparative Solubilities of Sulfadiazine, Sulfamerazine and Sulfamethazine and Their N₄ Acetyl Derivatives at Varying p_H Levels, *Proc Soc Exper Biol & Med* **53** 14 (June) 1943

3 Macartney, D W, Luxton, R W, Smith, G A, and Ramsey, W A. Sulfamethazine in the Treatment of Lobar Pneumonia (Seventy-Two Cases), *Lancet* **1** 639 (May 30) 1942

4 Peters, B A, and Easby, M L. Pneumonia Treated with Sulfamethazine (Seventy-Seven Cases), *Brit M J* **2** 230 (Aug 21) 1943. Pakenham-Walsh, R. Pneumococcal Meningitis Recovery with Sulfamethazine, *Lancet* **1** 649 (May 22) 1943

5 Jennings, P A, and Patterson, W H. Sulfamethazine. Clinical Trials in Children, *Lancet* **2** 308 (Sept 12) 1942

observations on the absorption, distribution and excretion of sulfamethazine in human beings. The fate of single doses of the drug varying in amount and administered by different routes was studied.

SUBJECTS AND METHOD

In the first part of the experiment patients with normal gastrointestinal, hepatic and renal function and without acute infectious diseases were selected as experimental subjects. An intake of 3,000 cc of fluid in twenty-four hours was encouraged. Records of intake and output were not kept routinely, but urinary specific gravity of 1.015 or below was used as the index of sufficient intake of fluid.

Each patient received a single dose of sulfamethazine differing either in amount or in method of administration, or in both. Single oral doses of 4, 3 and 1 Gm and intravenous doses of 5 and 3 Gm were given. The latter were administered in a 5 per cent solution of the sodium salt in sterile distilled water. For subcutaneous administration 3 Gm in 1,000 cc of isotonic solution of sodium chloride, a 0.3 per cent solution, was used. The drug was administered intramuscularly in the same concentrations as intravenously. Specimens of blood and urine were collected at intervals of one-half, one and two hours for the first twelve hours and then daily until the drug was excreted. Values for free and total sulfamethazine were estimated for each specimen. Whole blood was used for the determinations of the blood level.

In the second part of the experiment the effects on 19 patients with pneumonia of continuous administration of the drug were studied. Alkali therapy was not used.

A ABSORPTION AND EXCRETION OF SULFAMETHAZINE

1 *Results of Single Oral Doses* (tables 1 to 3) — Analysis of the fate of a single 4 Gm oral dose (table 1) shows rapid absorption. At one-half hour a value of 4 mg of free and 6 mg of total sulfamethazine per hundred cubic centimeters of blood was reached. The maximum, of 10.2 mg free and 11.3 mg total, was attained in two hours. Over the next eight hours the concentration gradually receded, becoming 5.1 mg free and 5.2 mg total at the twelve hour period and 2.75 mg free and 3.5 mg total at twenty-four hours. The percentage of acetylation varied between 19 and 33.3 in the first twelve hours, 11.5 per cent being the average. Subsequent values remained within these limits. Urinary concentrations were much higher than those of the blood, and most of the drug was excreted in the first twenty-four hours. The percentage of acetylation varied between 18 and 66.8, the average in the first twelve hours being 45 per cent.

Administration of the 3 Gm oral dose (table 2) illustrated experimentally something frequently observed

TABLE 1—*Absorption and Excretion of a Single 4 Gm Oral Dose of Sulfamethazine*

Date	Hours After Administration	Blood Levels		Per Cent of Acetylation	Urine Levels		Per Cent of Acetylation
		Free	Total		Free	Total	
12/1/43	½	4 0	6 0	33 3	14 4	35 0	58 9
	1	5 9	6 1	3 3	40 0	88 0	54 5
	2	10 2	11 3	9 7	129 0	174 0	25 9
	4	9 2	9 8	6 1	73 0	147 0	50 5
	6	6 9	8 2	15 0	33 0	46 3	28 8
	8	6 35	7 3	13 0	81 2	99 0	18 0
	10	5 9	6 5	9 2	95 0	222 0	57 2
	12	5 1	5 2	1 9	132 0	398 0	66 8
12/2/43	24	2 75	3 5	21 4	106 3	247 2	57 0
12/3/43	48	0 94	1 06	11 5	1 88	8 4	77 6
12/4/43	72	0 0	0 0	0 0	2 72	5 88	5 5
12/5/43	96	0 0	0 0	0 0	0 0	8 32	100 0

clinically, namely, unpredictable variations in individual patients. In the patient represented in table 2 a value

TABLE 2—*Absorption and Excretion of a Single 3 Gm Oral Dose of Sulfamethazine*

Date	Hours After Administration	Blood Levels		Per Cent of Acetylation	Urine Levels		Per Cent of Acetylation
		Free	Total		Free	Total	
12/ 6/43	½	7 2	7 3	1 4	8 0	13 2	39 4
	1	10 1	10 2	1 0	19 2	26 0	26 2
	2	10 5	12 2	13 9	10 3	18 4	44 0
	4	10 3	11 2	8 0	23 0	43 5	47 4
	6	8 5	11 5	26 1	24 0	45 0	46 7
	8	5 8	8 9	34 8	21 2	45 0	52 9
	10	5 2	8 6	39 5	16 8	29 2	42 5
	12	6 35	8 4	34 4	18 4	63 0	70 8
12/ 7/43	24	0 93	1 95	52 3	19 0	44 0	56 8
12/ 8/43	48	0 74	1 7	56 5	0	10 0	100 0
12/ 9/43	72	0 12	0 34	64 7	3 84	13 28	71 1
12/10/43	96	0	0	0	0	0	0

that is ordinarily considered a therapeutic level was attained in the surprising time of one-half hour—7 2 mg of free and 7 3 mg of total sulfamethazine. At one and four hours the levels were 10 1 mg and 10 3 mg free and 10 2 mg and 11 2 mg total respectively, with gradual recession as noted, only a trace remaining at the seventy-two hour period. The average percentage of acetylation in the first twenty-four hours was 18 6 in the blood and 46 3 in the urine.

After the 1 Gm oral dose (table 3) these values of acetylation were doubled, reaching an average of 35 5 per cent in the blood and 82 4 per cent in the urine.

TABLE 3—*Absorption and Excretion of a Single 1 Gm Oral Dose of Sulfamethazine*

Date	Hours After Administration	Blood Levels		Per Cent of Acetylation	Urine Levels		Per Cent of Acetylation
		Free	Total		Free	Total	
12/3/43	½	1 56	1 82	14 3	0 96	4 8	80 0
	1	2 02	3 1	34 8	1 04	10 64	90 2
	2	2 82	4 72	40 3	2 56	12 56	79 6
	4	2 88	5 86	50 9	0 96	5 6	82 9
	6	4 98	5 20	4 2	10 96	38 32	71 4
	8	3 28	3 86	15 0	9 20	50 6	81 8
	10	0 42	1 26	66 7	0 96	8 16	88 3
	12	0 62	1 18	47 5	3 76	73 2	94 9
12/4/43	24	0	0	0	1 52	7 36	79 3
12/5/43	48	0	0	0	0	20 56	100 0

The blood level showed a slower rise, to the peak level of 4 98 mg free and 5 2 mg total at six hours. There was a fairly rapid decline, with complete elimination in twenty-four hours.

2 *Results of Single Intravenous Doses* (tables 4 and 5)—Within one-half hour after intravenous administration of 5 Gm of sulfamethazine in 100 cc of distilled water (5 per cent solution) (table 4) the free

TABLE 4—*Absorption and Excretion of a Single 5 Gm Intravenous Dose of Sodium Sulfamethazine (5% Solution)*

Date	Hours After Administration	Blood Levels		Per Cent of Acetylation	Urine Levels		Per Cent of Acetylation
		Free	Total		Free	Total	
12/ 1/43	½	27 2	31 0	12 3	14 5	15 5	6 5
	1	23 1	29 0	20 3	107 0	200 0	46 5
	2	16 7	19 0	12 1	62 0	91 0	31 9
	4	20 8	22 7	8 4	100 0	206 0	51 5
	6	20 0	22 7	11 0	104 0	115 0	9 6
	8	20 4	23 1	11 7	121 0	323 0	62 5
	10	12 8	14 65	12 6	120 0	323 0	62 8
	12	10 8	11 1	2 7	168 0	400 0	53 0
12/2/43	24	5 7	6 8	16 2	8 4	23 6	64 4
12/3/43	48	1 4	1 5	6 7	9 44	38 8	15 7
12/4/43	72	0	0 42	100 0	0	16 48	100 0
12/5/43	96	0	0	0	0	0	0

drug level was 27 2 mg and the total 31 mg. At the end of twelve hours 10 8 mg free and 11 1 mg total remained in the blood. The twenty-four hour levels were 5 7 mg free and 6 8 mg total. Table 5 shows

TABLE 5—*Absorption and Excretion of a Single 3 Gm Intravenous Dose of Sodium Sulfamethazine (5% Solution)*

Date	Hours After Administration	Blood Levels		Per Cent of Acetylation	Urine Levels		Per Cent of Acetylation
		Free	Total		Free	Total	
12/ 6/43	½	11 9	12 6	5 6	32 8	40 0	18 0
	1	10 0	10 9	8 3	16 8	24 0	30 0
	2	10 6	10 7	0 9	14 8	36 0	58 9
	4	8 3	10 4	20 2	17 6	38 8	54 9
	6	9 3	10 0	7 0	27 2	35 6	23 6
	8	3 8	6 1	37 7	24 0	26 8	10 4
	10	6 1	7 15	14 7	16 8	24 4	31 1
	12	7 0	7 0	0	38 8	70 8	45 2
12/ 7/43	24	3 9	4 0	2 5	0 39	4 0	90 3
12/ 8/43	48	0 5	2 28	78 1	5 12	20 6	75 1
12/ 9/43	72	0 08	0 56	85 7	0	0	0
12/10/43	96	0	0	0	0	0	0

parallel results. The percentage acetylation values in the blood and the urine were within the same range as those which have already been discussed. Higher concentrations were noted at the six hour period than at the four hour period. This fact may possibly be due to loss of some of the drug in the preparation of the protein-free filtrate.

3 *Results of Single Subcutaneous Infusions* (table 6)—Three Gm of sodium sulfamethazine was given in a 0 3 per cent solution of sodium chloride (table 6). Blood levels were determined at one-half hour intervals during the three hour period of infusion and at two hour intervals for a twelve hour period afterward. In two hours the concentration of the drug in the blood was 61 mg per hundred cubic centimeters free and 65 mg total, it reached a peak in three and one-half hours of 112 mg free and 114 mg total and dropped to 4 mg free and 4 3 mg total at the twenty-four hour period. The percentage of acetylation was somewhat lower than after oral administration. The range varied from 17 per cent to 183 per cent, the average in the first six hours being 72 per cent and in the twenty-four hour period 93 per cent. The blood was free of the drug in seventy-two hours, but excretion continued through a one hundred and twenty hour period.

TABLE 6—*Absorption and Excretion of a Single 3 Gm Subcutaneous Injection of Sodium Sulfamethazine (0.3% Solution)*

Time, Hours	Blood Levels		Per Cent of Acetylation	Urine Levels		Per Cent of Acetylation
	Free	Total		Free	Total	
3/4	2.5	2.7	7.4			
1 1/2	1.6	4.2	14.3			
2	6.1	6.5	6.1	4.0	11.2	64.3
2 1/2	6.3	6.8	7.3	54.0	66.0	18.1
3	8.5	9.4	9.5			
3 1/2	11.2	11.4	1.7			
4	11.2	11.5	2.6	39.0	84.0	53.5
6	10.8	11.9	9.1	102.0	109.0	6.1
8	10.0	11.0	9.0	124.0	214.5	42.1
10	8.7	10.0	13.0	112.0	207.0	45.9
12	7.6	9.4	18.3	105.0	119.0	11.8
14	7.0	8.4	16.6	140.0	142.0	14.1
24	4.0	4.3	7.0	78.0	158.0	50.6
48	1.0	1.4		11.0	35.0	
72	0	0		2.0	13.4	
96				0	7.6	
120				0	10.8	

4 Results of Single Intramuscular Injection (table 7)
—Three grams of sodium sulfamethazine in a 5 per cent

TABLE 7—*Absorption and Excretion of a Single 3 Gm Intramuscular Injection of Sodium Sulfamethazine (5% Solution)*

Time, Hours	Blood Levels		Per Cent of Acetylation	Urine Levels		Per Cent of Acetylation
	Free	Total		Free	Total	
1	1.0	1.6	4.0	8.0	17.2	53.4
1 1/2	3.4	5.2	34.6			
2	5.4	7.4	32.4	48.0	146.0	67.1
4	4.7	6.4	28.0	53.0	121.0	56.2
6	3.4	5.8	41.3	41.0	156.0	73.7
8	2.0	4.7	57.4	56.0	285.0	80.3
10	1.4	3.5	60.0	41.0	255.0	80.0
12	1.2	3.4	65.0	26.5	200.0	86.7
24	0	0.4	100.0	8.4	248.0	96.6
48	0	0		0	0	

TABLE 8—*Effects of Continued Oral Administration of Sulfamethazine Dosage Schedule 4 Gm Initially and 1 Gm Every Four Hours*

	Date	Blood Levels		Per Cent of Acetyl- ation	Urine Levels		Per Cent of Acetyl- ation	Urine	
		Free	Total		Free	Total		pH	Specific Gravity
Case 1 J C hospital no 43 34910, a white man 60 yr old type III RML pneumonia total drug received 34 Gm afebrile course	7/29/43	Drug started							
	½ hr	0	11	100 0					
	1 hr	4 4	4 9	10 0	0	0 7	100 0	8 0	1 021
	2 hr	10 8	12 1	10 7					
	7/30/43	16 4	18 3	11 4	32 0	216 0	85 2	8 0	1 018
	7/31/43	15 7	16 7	6 0				6 0	
	8/ 2/43	8 4	9 5	11 4	280 0	950 0	70 5	5 0	1 020
	8/ 3/43	4 25	9 8	51 0					
	8/ 4/43	5 8	6 4	9 4	185 0	277 0	33 2	6 0	1 021
	8/ 6/43	0	0		12 0	19 4	38 1	6 0	1 013
Case 2 E L hospital no 43 35519, a 49 year old white man type VIII RLL pneumonia, total drug received 55 Gm febrile hr 32	7/31/43	Drug started							
	8/ 2/43	19 8	21 2	6 6	224 0	334 0	33 0	7 0	1 005
	8/ 3/43	6 9	9 7	28 9				8 0	1 007
	8/ 4/43	9 4	11 5	18 3	128 0	196 0	34 7	8 0	1 007
	8/ 5/43	5 3	7 6	32 6	73 0	94 2	22 5	5 0	1 009
	8/ 6/43	3 5	5 0	30 0	89 6	128 8	30 4	5 0	1 008
	8/ 9/43	Drug stopped							
	8/10/43	8 0	8 4	4 8				7 0	1 006
	Case 3 M S, hospital no 43 35690 a 26 year old colored woman with type VII LLL pneumonia total drug received 22 Gm febrile hr 22	8/ 2/43	Drug started						
8/ 3/43		12 0	13 1	8 4					
8/ 4/43		14 9	18 5	19 5	424 0	464 0	8 6	5 0	1 015
8/ 5/43		5 6	13 0	56 9	57 2	94 2	92 5	5 0	1 009
		Drug stopped							
Case 4 E L, hospital no 43 36285 a 50 year old man with type II RML pneumonia admitted with delirium tremens total drug received 32 Gm febrile hr 34	8/ 5/43	Drug started							
	1 hr	4 6	4 8	4 2					
	2 hr	7 6	8 1	6 2					
	8/ 6/43	13 8	14 9	7 4	69 2	85 6	19 2	8 0	1 009
	8/ 9/43	9 8	11 4	14 0				7 0	1 018
	8/10/43	11 65	12 0	2 9				7 0	1 010
	Drug stopped								
Case 5 M S, hospital no 43 36472, a 32 year old colored man with type I RLL pneumonia total drug received 26 Gm febrile hr 33	8/ 6/43	Drug started							
	15 min	4 2	5 1	16 6	1 2	2 8	57 1	4 0	1 015
	½ hr	4 4	5 1	18 7					
	1 hr	5 0	6 2	17 4	47 2	54 0	12 6	4 0	1 011
	8/ 7/43	3 0	9 9	69 7	63 2	74 2	14 8		
	8/ 9/43	9 4	18 4	48 9					
8/10/43	8 2	12 35	33 6						
	Drug stopped								
Case 6 A R hospital no 43 35703, a 28 year old colored man with Staphylococcus aureus RLL pneumonia, total drug received 26 Gm, febrile hr 36	8/ 2/43	Drug started							
	8/ 4/43	12 2	29 4	58 5	86 0	214 0	59 8	5 0	1 010
	8/ 5/43	8 9	20 4	56 4					
	8/ 6/43	5 1	16 3	68 7	74 8	101 2	26 1		
		Drug stopped							
Case 7 C L, hospital no 44 3889, a 26 year old colored woman with type I RML and RLL pneumonia total drug received 54 Gm febrile hr 72	1/27/44	6 68	13 7	51 2				6 0	1 016
	1/28/44	2 7	7 1	62 0				5 0	1 013
	1/31/44	3 2	8 5	62 4				6 0	1 010
Case 8 P B, hospital no 44 4275 a 44 year old colored man with type V RUL and RML pneumonia complicated by toxic hepatitis nephritis and pericarditis, icteric index 37 total drug received 70 Gm	1/31/44	Drug started							
	2/ 1/44	11 4	22 1	48 4		Many granular casts		4 5	1 017
	2/ 3/44	8 4	17 4	51 7		Occasional cast		4 5	1 016
	2/ 5/44	7 2	10 3	30 1		Occasional cast		5 0	1 016
	2/ 7/44	3 7	7 5	50 7		Occasional cast		4 5	1 003
	2/ 8/44	3 2	8 5	62 4		Occasional cast		5 0	1 020
	2/11/44	2 97	4 3	30 9				5 0	1 016
		Drug stopped							
	2/15/44	0	1 6	100 0				5 5	1 013

solution of sodium chloride was given intramuscularly. Within two hours the blood contained 5.4 mg free and 7.4 mg total drug per hundred cubic centimeters. This was the peak level, following which there was a rapid fall, with complete excretion of the drug by the end of twenty-four hours. This was a much lower concentration than that following administration by other routes. Acetylation closely paralleled that following the single 3 Gm oral dose, 28 per cent being the average in the first six hours and 47 per cent the average in twenty-four hours, the range was 4 to 100 per cent.

5 *Results of Multiple Doses* (tables 8-10).—Nineteen patients with pneumonia were treated with sulfa-

morning dose. The specimens from patients on the six hour schedule were obtained three to four hours after the last morning dose. At times variations in blood level occurred in patients in the same groups and in the same patient on different days. In general, a higher concentration was maintained during the first few days, and this was followed by a drop to a level which remained constant as long as the drug continued to be administered.

The fall in blood level noted in patients with pneumonia may have been due to fluid balance, however, as this factor was kept fairly constant,

TABLE 9—*Effects of Continued Oral Administration of Sulfamethazine Dosage Schedule 3 Gm Initially and 1 Gm Every Six Hours*

	Date	Blood Levels		Per Cent of Acetyl-ation	Urine Levels		Per Cent of Acetyl-ation	Urine	
		Free	Total		Free	Total		pn	Specific Gravity
Case 9 M T, hospital no 43 44055, a 25 year old colored woman with atypical pneumonia in LLL, total drug received 25 Gm, febrile hr 47	9/27/43	Drug started							
	1/2 hr	1.85	1.85	0					
	1 hr	10.75	10.8	4.6					
	2 hr	13.5	14.8	8.8	38.8	54.4	28.7		
	3 hr	15.4	16.6	7.2	22.4	24.8	9.7		
	5 hr	14.2	16.3	17.2	69.2	95.6	27.6		
	7 hr	15.0	17.2	12.8	150.0	276.8	45.9		
	9/28/43	14.4	17.0	15.3					
	9/29/43	15.5	17.0	8.8	454.0	512.4	11.4	4.0	1.011
	9/30/43	14.6	17.9	18.4	146.0	240.0	39.3	5.0	1.011
	10/ 1/43	7.7	12.1	26.4	200.0	329.0	39.2	4.0	1.010
	10/ 4/43	1.92	2.48	22.6	16.8	28.8	41.7	5.0	1.011
	10/ 6/43	0	0		0	0		7.0	1.010
Case 10 M S, a 26 year old white woman with LLL pneumonia, total drug received 17 Gm, febrile hr 56	9/19/43	Drug started							
	9/20/43	3.0	5.4	44.4				5.0	1.014
	9/21/43	1.54	3.96	61.1				8.0	1.010
	9/22/43	1.7	4.1	53.5				8.0	1.006
	9/23/43	Drug stopped							
Case 11 R J, hospital no 43 47247, a 60 year old white woman with RML pneumonia, patient had a toxic thyroid, auricular flutter occurred during the course of infection and subsided spontaneously, total drug received 18 Gm, febrile hr 24 BMR, plus 43	10/18/43	Drug started							
	10/19/43	8.7	11.1	21.6				5.0	1.013
	10/20/43	9.8	10.8	9.3				5.0	1.009
	10/21/43	10.2	13.0	21.5					
	10/22/43	7.9	9.2	14.1				6.0	1.010
	10/23/43	Drug stopped							
	10/25/43	0	1.55	100.0				4.0	1.009
Case 12 W G, hospital no 43 42749, a 54 year old colored man with type VII RUL, RML and RLL pneumonia and bacteremia total drug received 26 Gm febrile hr 38	9/18/43	Drug started							
	15 min	3.14	3.2	1.9					
	1/2 hr	3.22	3.42	5.8	8.72	10.64	18.0	5.0	1.025
	45 min	3.66	4.38	16.4					
	1 hr	4.36	4.94	11.7					
	2 hr	4.68	5.06	7.5					
	3 hr	4.84	5.40	10.4					
	4 hr	7.0	8.8	20.5					
	5 hr	7.2	9.1	20.9					
	6 hr	7.5	9.1	17.6					
	7 hr	6.4	8.1	21.0					
	9/20/43	6.5	13.4	51.5	105.2	116.6	9.8	5.0	1.019
	9/21/43	14.1	17.0	17.1	132.4	295.2	63.8	6.5	1.010
	9/22/43	8.1	9.5	14.7	77.2	106.0	27.2	4.5	1.011
	9/23/43	7.8	8.7	10.3	78.4	100.4	21.9	6.0	1.013
	9/24/43	6.7	10.0	49.0					
	9/27/43	Drug stopped							
Case 13 H D, hospital no 44 6836 a 31 year old Indian with type VII RUL, RML and RLL pneumonia and bacteremia total drug received 22 Gm orally and 3 Gm intravenously seven febrile days	2/16/44	Drug started							
	2/18/44	2.0	5.2						
	2/19/44	0	1.3						
	2/20/44	200,000 units type VII serum, urticaria reaction							
	2/21/44	Blood culture positive, 3 Gm intravenously							
	2/22/44	4.9	5.7	14.0				4.5	1.005
	2/23/44	1.1	3.0	60.3				5.0	1.009
	2/24/44	1.9	4.0	72.5				6.0	1.009
	2/25/44	0	2.9	100.0				5.0	1.009

methazine for different periods of time and on the following schedules of dosage: group 1, 4 Gm as the initial dose and 1 Gm every four hours (table 8), group 2, 3 Gm as the initial dose and 1 Gm every six hours (table 9), group 3, 3 Gm as the initial dose and 1 Gm every eight hours (table 10). The concentrations of the drug in the blood and in the urine of patients in each group were estimated daily. The time of collection of the specimens of blood and urine could not be kept constant. With the four and eight hour schedules the specimens were collected one to two hours after the last

it seems most plausible that a fall in blood level occurred with lessening of the infection, as was indicated by the concomitant improvement of the patients. Is fever a possible factor in increasing absorption of the drug? It is known from laboratory experiments that the speed of any chemical reaction is increased with heat.

Weight and sex are factors which may modify the action of drugs. No difference was noted

between men and women in this short series. Records of weight were not kept, but our impression is that it is a negligible consideration. A definite influence in the absorption and excretion of the drug is the state of the kidneys (table 11). Our patients with toxic nephritis, as shown by an elevated level of nonprotein nitrogen and at times of creatinine, absorbed the drug as readily as the others but showed a higher percentage of acetylation. The level of the conjugated drug varied from 21.3 to 64.1 per cent, with an average of 50 per cent, in these patients.

product. In this study two different shipments of sulfamethazine were used, one in 1943 and the other in 1944. This fact is mentioned because of the marked difference in average concentrations in the blood obtained with the two lots. The average level of free drug obtained in 1943 from patients on the four, six and eight hour schedules was 12.8, 9.1 and 8.4 mg respectively per hundred cubic centimeters of blood. The level obtained in 1944 was 5.4, 5 and 4.1 mg. Thus the values for 1944 were one-half to one-third lower than those for 1943. The reasons for this are not apparent. From a clinical stand-

TABLE 10—Effects of Continued Oral Administration of Sulfamethazine Dosage Schedule 3 Gm Initially and 1 Gm Every Eight Hours

	Date	Blood Levels		Per Cent of Acetyl ation	Urine Levels		Per Cent of Acetyl ation	Urine	
		Free	Total		Free	Total		pH	Specific Gravity
Case 14 C M, hospital no 43 44445, a 40 year old white woman with LLL pneumonia of undetermined cause total drug received 21 Gm febrile 4½ days	9/30/43	Drug started							
	½ hr	8.5	8.7	2.3					
	1 hr	9.2	9.8	6.1	13.2	18.4	28.3		
	3 hr	11.9	15.2	21.7	30.0	35.6	15.7		
	5 hr	15.6	17.2	9.3	34.0	48.4	29.8		
	7 hr	15.5	18.2	14.8	54.8	94.0	41.7		
	9 hr	17.0	18.6	8.6	38.8	52.4	26.0		
	10/ 1/43	12.1	15.0	19.3	151.2	284.0	46.8	8.0	1.011
	10/ 4/43	10.3	12.4	16.9	194.0	216.4	10.4	5.0	1.014
	10/ 5/43	9.3	10.9	14.7	206.0	362.0	4.1	5.0	1.014
Case 15 E K hospital no 44 4561 a 67 year old colored man with type III RLL pneumonia, total drug received 20 Gm febrile hr 72, NPN 85 creatinine 2.7 WBC on admission 2,100 with 71% polymorpho nuclear neutrophils, rose to 8,300 on therapy	1/31/44	Drug started							
	2/ 3/44	10.1	19.2	47.4				4.5	1.020
	2/ 5/44	4.2	11.7	61.1				4.5	1.021
	2/ 6/44	Drug stopped							
	2/ 7/44	0.6	2.8	78.6				8.0	1.011
Case 16 L B hospital no 44 4138, a 36 year old colored man with type VIII RLL pneumonia total drug received 11 Gm 4 febrile days	1/28/43	Drug started							
	1/31/43	2.5	6.0	58.3				5.0	1.013
	2/ 1/43	3.4	4.6	26.1				4.5	1.015
	2/ 3/43	2.3	5.7	57.5				8.0	1.012
		Drug stopped							
Case 17 O A hospital no 44 4351 a 43 year old colored man with type III RLL and RML pneumonia total drug received 13 Gm orally and 3 Gm intravenously febrile hr 57	1/30/44	Drug started, 3 Gm intravenously							
	2/ 1/44	3.0	6.9	56.5				5.0	1.005
	2/ 3/44	2.5	3.2	21.9				4.5	1.006
	2/ 4/44	Drug stopped							
	2/ 5/44	0	0.6	100.0					
Case 18 L G hospital no 44 4991, a 56 year old colored man with type VIII RLL and LLL pneumonia, total drug received 41 Gm orally and 6 Gm intravenously 8 febrile days	2/ 3/44	Drug started							
	2/ 7/44	3.3	4.6	28.3					
	2/ 8/44	9.2	10.1	8.9					
	2/11/44	4.4	6.6	33.3				5.5	1.013
	2/14/44	4.7	5.5	14.5				6.5	1.014
	2/15/44	5.3	5.6	5.4				6.0	1.019
Case 19 H L, hospital no 44 5048, a 40 year old colored man with RLL pneumonia of undetermined cause NPN 46 total drug received 31 Gm febrile hr 98	2/ 3/44	Drug started							
	2/ 7/44	4.3	4.3	0				4.5	1.020
	2/ 8/44	5.8	6.4	9.4				5.0	1.019
	2/10/44	Drug stopped							
	2/11/44	2.97	3.0	1.0				5.0	1.019

TABLE 11—Absorption in Toxic Nephritis

Nonprotein Nitrogen	Creatinine	Blood Levels		Per Cent of Acetylation
		Free	Totals	
67	2.2	3.2	7.0	54.3
		9.6	12.2	21.3
		11.4	22.8	50.0
80	2.7	8.4	17.4	51.6
		10.1	19.2	47.4
		4.2	11.7	64.1
92	5.1	8.9	20.4	56.3
55	1.5	9.3	22.9	59.3
		9.6	15.8	45.5

point the results in 1944 were as good as those in 1943. The patients treated in 1944 had infections that were in some respects more severe, which would indicate even better results. In the light of increasing experience the necessity of daily determinations of blood levels of clinical patients may be reasonably questioned. We regard 7 to 10 mg per hundred cubic centimeters of blood as a therapeutic level, but we know that many infections respond clinically on lower levels and that many fail to respond to consistently high levels. It would seem sufficient to limit calculations of drug levels to those

Another factor, which may not ordinarily have to be considered, is the lack of a standardized

patients who do not make a response in forty-eight to seventy-two hours—those with complicating diseases which may hinder good absorption and those with overwhelming infections

Percentage acetylation varied so greatly in both the blood and the urine that average values are of little significance. In general the percentage was much higher in the urine than in the blood. At no time were any crystals of sulfamethazine noted in the urine.⁶ Because of shortage of personnel the twenty-four hour urines could not be collected and the percentage of total daily excretion calculated.

B DISTRIBUTION OF SULFAMETHAZINE IN VARIOUS BODY FLUIDS (TABLES 12 AND 13)

1 *Cerebrospinal Fluid* (table 12)—Sulfamethazine is readily absorbed in the cerebrospinal fluid, reaching an average concentration of 42.4 per cent of the blood

TABLE 12—Sulfamethazine Concentration in Various Body Fluids

Blood		Per Cent of Acetylation	Spinal Fluid		Per Cent of Acetylation	Per Cent of Blood
Free	Total		Free	Total		
3.0	11.9	64.7	5.9	7.8	23.1	196.6
Taken 3 hr. after 3 Gm. intravenously						
4.0	4.0	0	1.6	2.0	20.0	40
8.0	17.0	52.9	4.0	5.5	27.3	50
2.7	5.9	54.2	0.7	0.7	0	26
2.8	6.6	57.6	1.5	2.1	28.6	53.5
			5.3	10.5	49.5	
Blood			Gastric Juice			
7.3	9.4	22.3	1.3	1.6	18.8	18
0.9	3.7	75.7	0	7.6	100.0	
8.0	9.2	13.0	4.4	5.6	21.4	55
Blood			Pleural Fluid			
7.3	9.4	22.3	5.2	12.0	56.7	71
			9.8	13.4	26.9	

level, with a range between 26 and 53.5 per cent. For 1 patient, for whom figures were not included in the average, a concentration in the spinal fluid twice that in the blood was obtained. This phenomenon has been reported by others.³ The percentage of acetylation was much less in the spinal fluid, about half that in blood taken at the same time.

2 *Gastric Juice* (table 12)—In 2 patients there was concentration in the gastric juice equal to 18 and 55 per cent respectively of the concentration in the blood. In a third patient no free drug was absorbed into the gastric secretion and the total value was 7.6 mg. The percentage of acetylation varied and was either higher or lower than that of the blood.

3 *Pleural Fluid* (table 12)—For only 1 patient was there an opportunity to determine the ratio of absorption into the pleural fluid to absorption into the blood, and this was 71 per cent.

4 *Fractionated Blood Levels* (table 13)—Simultaneous concentrations were done on whole blood, plasma and erythrocytes of 8 patients who were receiving mul-

tiples doses. The concentration in the plasma was much higher than in the whole blood. The concentration in the red blood cells was much lower than that reported for sulfamerazine and sulfadiazine, varying from 0 to 1.5 mg. per hundred cubic centimeters.

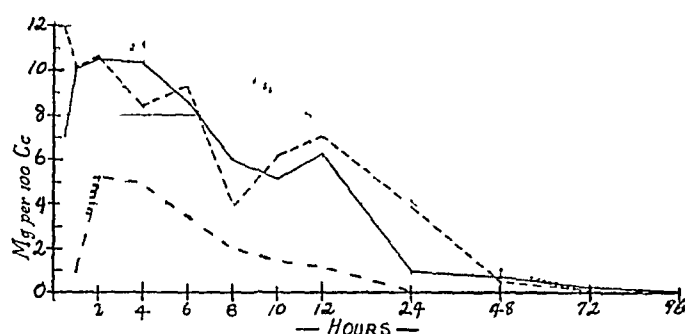
TABLE 13—Fractionated Blood Levels

Whole Blood			Plasma			Red Blood Cells			Vol. per cent
Free	Total	Per Cent Acetylation	Free	Total	Per Cent Acetylation	Free	Total	Per Cent Acetylation	
8.4	9.5	11.6	21.2	23.1	8.2	0			38.7
4.8	9.8	51.0	8.0	15.0	46.7	0.5	1.65	69.7	43.6
19.8	21.2	6.6	23.2	25.0	7.2		Trace		41.1
6.9	9.7	28.9	9.75	13.5	27.8	0.5	1.25	60.0	35.1
12.0	13.1	8.4	14.1	17.1	17.5	0	0		34.8
10.3	12.4	16.9	13.3	15.8	15.8	1.5	1.96	23.5	34.8
15.5	17.0	8.8	21.6	24.6	12.2	0	0		35.2
7.8	8.7	10.3	10.5	10.7	1.9	0.5	0.76	34.2	36.2

COMMENT

Comparing these results with the studies of Murphy and co-workers⁷ and with our own observations on sulfamerazine,⁸ we observed that sulfamethazine is absorbed from the gastrointestinal tract more rapidly than sulfamerazine and just as completely. Adequate concentrations in the blood are maintained with the same schedules of dosage as for sulfamerazine.

The parenteral routes of administration gave expected results. Intravenous injection produced immediate high concentrations, subcutaneous injection induced a blood level in three hours equal to that obtained in one hour by oral ingestion. Administration by the intramuscular route resulted in rapid but less complete absorption. Regardless of the type of parenteral administration, after the three hour period the decreases in concentration of sulfamethazine in the blood ran parallel (chart).



Absorption of sulfamethazine following a single 3 Gm dose (oral administration, solid line, intramuscular [5 per cent solution], dash line, subcutaneous [0.3 per cent solution], dotted line, intramuscular [5 per cent solution], dot and dash line).

7 Murphy, F. D., Clark, J. K., and Flippin, H. F. Studies on 2-Sulfanilamide-4-Methylpyrimidine (Sulfamerazine, Sulfamethyldiazine) in Man. Absorption, Distribution and Excretion, *Am. J. M. Sc.* **205**: 717 (May) 1943.

8 Volini, I. F., Engbring, G. M., and Schorsch, H. A. Sulfamerazine. Studies on Absorption, Distribution, Excretion and Toxicity with Clinical Applications, *Proc. Chicago Soc. Int. Med.*, Nov. 22, 1943.

6 Lehr, E., and Antopol, W. Typical Urinary Crystals of Three Sulfanilamide Derivatives Produced in vitro, *Science* **94**: 282 (Sept. 19) 1941. Sulfonamides and the Renal Tract, editorial, *Lancet* **1**: 651 (May 22) 1943.

Sulfamethazine penetrates as readily into body fluids as do sulfamerazine and sulfadiazine. The rate of excretion of sulfamethazine is about the same as that of sulfadiazine and somewhat more rapid than that of sulfamerazine. It is at its maximum in the first twenty-four hours.

The percentage of acetylation in the blood varies, average values are slightly higher than those observed for sulfamerazine. The percentage of conjugation in the urine is much higher than that in the blood, as is generally observed for all the sulfonamide compounds.

There were no unfavorable reactions to the drug in this series. No crystalluria was observed. The complete lack of urinary complications is explained by the greater degree of solubility of

sulfamethazine in its free and acetylated forms in the entire range of urinary p_H .

SUMMARY

The absorption, distribution and excretion of sulfamethazine were studied after single doses were administered to patients with noninfectious diseases and multiple doses to patients with pneumonia.

Like sulfamerazine, sulfamethazine is effective in smaller and fewer doses than sulfadiazine. It is more readily absorbed and maintains levels equal to those of sulfamerazine.

No unfavorable reactions to the drug occurred.

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OCCLUSION OF THE HEPATIC VEINS

A REVIEW OF TWENTY CASES

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Occlusion of the hepatic veins apparently may be caused by disease of the veins themselves or may occur secondarily to inflammatory, cirrhotic or neoplastic changes in the liver, thrombosis in the neighboring vena cava, polycythemia vera or debilitating disease in which the circulation is slowed. The obstruction is usually due to thrombosis, but some investigators have expressed the view that it is developmental.

Occlusion of the hepatic veins leads to congestion and atrophy of the liver. Usually the region of congestion is not large enough to produce recognizable symptoms. If symptoms do arise they usually are masked by the more profound changes of the primary disease. Rarely, the process is sufficiently disturbing and encompassing to produce portal hypertension and even hepatic failure. The syndrome may develop slowly or rapidly. The outstanding clinical features are pain in the upper part of the abdomen and the back, an enlarged tender liver with latent or mild jaundice, an enlarged spleen, well developed collateral circulation and ascites (portal hypertension). The disturbance of hepatic function is marked. Thrombosis of the hepatic veins may be followed by thrombosis of the portal and mesenteric veins and infarction of the bowel. Hepatic coma, rupture of esophageal varices, carcinoma or intercurrent infection is the immediate cause of death.

Occlusion of the hepatic veins is also known as endophlebitis obliterans hepatica and Chiari's disease. Budd¹ is credited with reporting the first case of primary obstruction of the hepatic veins. In 1899, Chiari² collected 7 cases from the literature and added 3 of his own in which the occlusion was thought to be due primarily to

inflammation of the wall of the vein itself. He established primary occlusion of the hepatic veins as a disease entity. The diagnosis is usually made at necropsy. Baehr and Klemperer³ have stated that Oppenheimer made the diagnosis in a case reported by them and that the diagnosis was confirmed at necropsy. East⁴ made a clinical diagnosis, but it was not confirmed by exploration or by necropsy. A review of the case records herein given and of the cases reported by other authors leads us to believe that the diagnosis should at least be suspected in a greater number of cases than in the past.

INCIDENCE

Occlusion of the hepatic veins apparently is rare. According to Kahn and Spring⁵ only about 60 cases in which the occlusion was the major cause of the patient's illness were reported in the literature prior to 1940. The condition has been rare at the Mayo Clinic. Review of the records of all cases in which necropsy was done at the clinic from 1910 to 1939 inclusive has disclosed 20 cases of occlusion of the hepatic veins. In 16 cases the occlusion was an incidental finding at necropsy and had not produced any recognizable symptoms. In the remaining 4 cases it had caused symptoms, and in 3 of these it had unquestionably contributed to or been the chief cause of death. In all 20 cases the occlusion was due to thrombosis.

CAUSATION

Occlusion of the hepatic veins may be primary or secondary to disease in other parts of the body. Primary occlusion is rare, but explanations for

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1 Budd, G. Diseases of the Liver, ed 3, Philadelphia, Blanchard & Lea, 1857, p 195.

2 Chiari, H. Ueber die selbständige Phlebitis obliterans der Hauptstämme der Venae hepaticae als Todesursache, Beitr z path Anat u z allg Path 26 1-18, 1899.

3 Baehr, G, and Klemperer, P. Thrombosis of the Portal and of the Hepatic Veins, M Clin North America 14 391-410 (Sept) 1930.

4 East, T. Chiari's Disease, with Hypertrophic Osteoarthropathy and Familial Lipomatosis, Proc Roy Soc Med 26 272 (Nov) 1932.

5 Kahn, S, and Spring, M. Thrombosis of the Hepatic Veins—Chiari's Syndrome. Report of a Case with Biopsy and Venous Pressure Determination, Ann Int Med 14 1075-1083 (Dec) 1940.

its occurrence are multiple. These have been summarized by Thompson and Turnbull⁶ and more recently by Hutchison and Simpson.⁷ Chiari advanced the hypothesis that the occlusion is due to a primary inflammation of the vein with or without thrombosis. He thought that the process is syphilitic, but present day evidence does not support this view. A secondary hypothesis, namely, that the occlusion is due to primary thrombosis and that the inflammatory changes in the wall are secondary, has been supported by Thompson and Turnbull. The retardation of, or even the reversal of, the flow of blood at the diaphragmatic opening of the inferior vena cava caused by increase of pressure in the thorax or occurrence of eddies in the ostiums of hepatic veins where the blood streams of the hepatic veins and of the inferior vena cava converge have been cited as possible explanations of development of thrombosis in this area. A third, the mechanical, hypothesis was advanced by Kretz,⁸ who expressed the view that the liver is to some extent suspended by the hepatic veins, that stress on the veins results in mechanical damage and that the resulting scar tissue occludes the ostiums of the veins. A fourth, the congenital, hypothesis was first advanced by Rosenblatt,⁹ in 1867. He suggested that the fibrosis of fetal interstitial hepatitis prevents union between the hepatic veins and the inferior vena cava or occludes the hepatic veins by pressure. It has also been suggested that stricture at the point of junction of the hepatic veins and the inferior vena cava might be developmental. Moor¹⁰ in 1902 suggested that the tendency to obliterative processes in this region seen in the obliteration of the ductus venosus might remain latent but might subsequently be reactivated by some irritant and involve the hepatic veins. Hutchison and Simpson in 1930 pointed out another possible developmental hypothesis, namely, that the intrauterine process of obliterating many of the venae revehentes might progress too far. The choice of any one cause seems to have little practical in-

terest, as a preventive approach seems out of the question at this time.

Occlusion of the hepatic veins is more often due to thrombosis secondary to disease elsewhere than to primary disease of the veins themselves. The cause of secondary occlusion of the hepatic veins is usually found in the liver, but the occlusion may be attributable to extrahepatic conditions. The most frequent intrahepatic causes are inflammatory, neoplastic and cirrhotic processes. These processes predispose to thrombosis by injury of the intima of the vein or by slowing of the circulation through pressure on and narrowing of the lumen of the vein. Gummas and hydatid cysts are less frequent causes of thrombosis of the hepatic veins.¹¹ Among the extrahepatic causes of secondary thrombosis of the hepatic veins may be mentioned (1) trauma¹², (2) perihepatitis¹¹, (3) scars¹¹, (4) thrombosis of the inferior vena cava, especially malignant thrombosis¹¹, (5) constrictive pericarditis¹¹, (6) diseases which cause multiple thrombosis, such as polycythemia vera¹⁵ and thrombophlebitis migrans,³ and (7) entrance of malignant or infectious particles into the hepatic veins, owing to reversal of the flow of blood during coughing or straining in carcinoma of the thyroid gland or abscess of the brain or of a lung.¹¹

PATHOLOGIC ANATOMY

Thrombosis of the hepatic veins may involve all or any of them and may even extend into the vena cava. The thrombi often indicate the factors producing them, thus, they may be purulent or contain malignant tissue. Depending on the duration of life after thrombosis occurs, the clots may undergo organization and canalization. When repeated thrombosis occurs, thrombi are usually superimposed on one another. The wall of the vessel reacts by marked fibrous thickening, especially the intima. A variable but usually small

6 Thompson, T, and Turnbull, H M. Primary Occlusion of the Ostia of the Hepatic Veins, *Quart J Med* **5** 277-296 (Jan) 1912.

7 Hutchison, R, and Simpson, S L. Occlusion of the Hepatic Veins with Cirrhosis of the Liver, *Arch Dis Childhood* **5** 167-186 (June) 1930.

8 Kretz, R. Pathologie der Leber, *Ergebn d allg Path u path Anat* **8** 498, 1902.

9 Rosenblatt, O G. Ueber einen Fall von abnormen Verlauf der Lebervenen in Verbindung mit Cirrhose und Carcinom der Leber und consecutiver carcinomatöser Infiltration des Peritoneums, *Jahresb u d Leistung d ges Med* **1** 226-227, 1867.

10 Moore, F C. Primary Obliterative Inflammation of the Main Trunks of the Hepatic Veins, *M Chron* **3** 240-251, 1902.

11 Rolleston, H, and McNee, J W. *Diseases of the Liver, Gallbladder and Bile Ducts*, ed 3, London: The Macmillan Company, 1929.

12 Hess, A F. Fatal Obliterating Endophlebitis of the Hepatic Veins, *Am J M Sc* **130** 986-1001 (Dec) 1905.

13 Altschule, M D, and White, G. Chiari's Syndrome in a Patient with Polycythemia Vera, *New England J Med* **220** 1030-1033 (June 22) 1939.

14 Hallock, P, Watson, C J, and Berman, L. Primary Tumor of Inferior Vena Cava with Clinical Features Suggestive of Chiari's Disease, *Arch Int Med* **66** 50-61 (July) 1940.

15 (a) Altschule and White¹³ (b) Norman, I L, and Allen, E V. The Vascular Complications of Polycythemia, *Am Heart J* **13** 257-274 (March) 1937. (c) Solval, A R. Hepatic Complications in Polycythemia Vera, with Particular Reference to Thrombosis of the Hepatic and Portal Veins and Hepatic Cirrhosis, *Arch Int Med* **62** 925-945 (Dec) 1938.

number of inflammatory cells are scattered through the wall, which contracts and further causes stenosis of the lumen. Possibly such a final stage may produce the picture which Chiari and others called endophlebitis obliterans hepatica. Occasionally the hepatic veins are only cords of fibrous tissue.¹⁶ In 1 case the lumen of the vena cava was separated from the lumen of a hepatic vein by a thin membrane.

The pathologic changes in the liver vary with the acuteness or the chronicity of the process. Acute thrombosis of the portal vein has been produced experimentally, and the observations made have been highly instructive. In dogs complete, sudden hepatic obstruction by constriction with a rubber band causes marked congestion and enlargement of the liver, with necrosis due to central pressure and with hyaline thrombi in the central veins.¹⁷ In human beings, in the few cases reported of acute, spontaneous thrombosis of the hepatic veins,¹⁸ the liver has been extremely congested, purplish and smooth, in 1 case it weighed more than 2,500 Gm. Wedge-shaped regions characterized by this congestive change occur if single tributaries are obstructed. Microscopically, the central veins are distended or thrombosed. The sinusoids are packed with erythrocytes, which may be conglomerated. Hemorrhage from the central veins and necrosis caused by pressure sometimes involve almost the entire lobule. A few inflammatory cells are seen. The changes are those of an infarct of Zahn instead of complete necrosis, such as occurs in true infarction of the liver.

Chronic obstruction of the inferior vena cava with subsequent hepatic obstruction occurring in monkeys causes venous congestion and central degeneration of hepatic lobules without fibrosis, together with ascites.¹⁹ In cats with hepatic obstruction the central necrotic cells disappear and are replaced by dilated sinusoids without fibrosis.²⁰ In human beings central congestion with enlargement of the liver may be replaced by atrophy in the more chronic forms of

the disease. In some cases the liver has been found to weigh as little as 950 Gm.¹² and to be nodular. Actually, all degrees of congestion, central necrosis, atrophy and collapse fibrosis are seen. Occasionally, several different stages may be seen in the same liver. Thus, in case 4, to be reported in subsequent paragraphs, the left lobe of the liver was almost completely atrophic, the right lobe, in which some patches of atrophy were present, was acutely congested, and the caudate lobe, which was free from involvement had undergone compensatory hypertrophy. Although distortion from extensive central necrosis and resorption is present, the lobular architecture is maintained, as has been stated. True regeneration of hepatic tissue does not occur, but compensatory hypertrophy of the uninvolved parenchyma is common. Cirrhosis and even primary carcinoma of the liver have been reported as late results.²¹

Thrombosis of the hepatic veins produces portal hypertension with ascites and splenomegaly (chronic passive congestion). Thrombosis of the portal and mesenteric veins may follow. Collateral circulation of the portal system may be well developed.

ASYMPTOMATIC THROMBOSIS

When thrombosis of the hepatic veins is found incidentally at necropsy the condition, because of its relative unimportance, is seldom reported in the literature or mentioned in the report of the observations at necropsy. The thrombosis usually is not extensive, or it has existed long enough for canalization to have occurred and for an adequate collateral circulation to have become established.

As was previously stated, in 16 of the 20 cases in our series the condition was asymptomatic and was found incidentally at necropsy (table 1). In cases 5 to 12 inclusive the condition followed hepatic inflammation, abscesses of the liver were found in 7 of the 8 cases. In 2 of these cases the abscesses were actinomycotic, and in another case the abscesses were secondary to pyelophlebitis. In 1 case multiple abscesses were associated with metastatic carcinoma, but the purulent character of the thrombosis was indicative of its origin. In case 12 thrombosis apparently was the result of purulent cholangitis. In cases 13, 14, 15 and 16 metastatic carcinoma of the liver had injured the walls of the hepatic veins or had invaded the veins and produced throm-

16 Osler, W., cited by Thompson and Turnbull.⁶

17 (a) Simonds, J. P., and Callaway, J. W. Anatomical Changes in the Livers of Dogs Following Mechanical Constriction of the Hepatic Veins, *Am J Path* 8 159-166 (March) 1932. (b) Simonds, J. P. and Jergesen, F. H. Late Changes in Liver Induced by Mechanical Obstruction of the Hepatic Veins, *Arch Path* 20 571-581 (Oct.) 1935.

18 Thompson and Turnbull.⁶ Altschule and White.¹³ Sohval.^{15c}

19 Bolton, C. The Pathological Changes in the Liver Resulting from Passive Venous Congestion Experimentally Produced, *J Path & Bact* 19 258-264, 1914.

20 Bolton, C., and Barnard, W. G. The Pathological Occurrences in the Liver in Experimental Venous Stagnation, *J Path & Bact* 34 701-709 (Nov.) 1931.

21 Budd.¹ Chiari.² Kretz.⁸ Rosenblatt.⁹ Nishikawa, Y. Ueber die Obliteration der Stammleberenen und des hepatischen Hohlvenenabschnittes (Thrombophlebitis obliterans venae hepaticae et venae inferioris), *Mitt a d med Fak d k Univ zu Tokio* 20 151-305, 1918-1919.

bosis In case 17, which is especially interesting, portal cirrhosis was present Large regenerating nodules, which had caused distortion and constriction of the hepatic veins, apparently had caused thrombosis In cases 18, 19 and 20 systemic slowing of the circulation seems to be the best explanation for the thrombosis, as there were no lesions in the liver to account for the condition General peritonitis was found in 2

systemic slowing of the circulation in thrombosis of the hepatic veins was clearly demonstrated in these cases

SYMPTOMATIC THROMBOSIS

In cases in which thrombosis of the hepatic veins has produced symptoms, thrombosis may play the major or the only role in the causation of symptoms and death The onset and the progression of the disease may be acute or chronic

Observations at Necropsy in Sixteen Cases in Which Thrombosis of the Hepatic Veins Was Present

Case	Age, Yr	Sex	Cause of Death	Liver	Hepatic Veins	Other Thrombosis
5	36	♂	Cholecystitis (stones), abscesses of liver, purulent pericarditis	Multiple large abscesses patches of congestion	Wall of a medium vein partly destroyed by abscess, pus in lumen	Inferior vena cava, pulmonary infarcts (emboli?)
6	65	♀	Carcinoma of gallbladder obstructing hepatic ducts, hepatic insufficiency	Dilated bile ducts, multiple abscesses and carcinomatous nodules, patchy congestion	Puriform thrombus, extending into vena cava	
7	54	♀	Cholecystitis, choledocholithiasis, suppurative pyelophlebitis	Multiple pyelophlebitic abscesses	Septic thrombi of 1 medium vein and several small veins	Pyelophlebitis, right femoral vein
8	54	♂	Duodenal ulcer abscesses of peritoneum, liver and lung	Abscess in left lobe (4 cm)	Septic thrombus in a medium vein, extending from abscess	Intrahepatic portal vein right saphenous vein, mural thrombus in right ventricle
9	56	♂	Staphylococcal abscesses of liver, lungs and right kidney, origin not known	Multiple abscesses (1 to 7 cm)	Thin mural organizing thrombus extending into vena cava	Inferior vena cava, left femoral vein right renal vein, a medium intra hepatic vein
10	19	♂	Actinomycosis of liver, lungs and right kidney	Abscess of right lobe (13 cm)	Purulent thrombus in medium vein, extending from abscess	Inferior vena cava right renal vein, both iliac veins
11	22	♂	Actinomycosis of liver, lungs and spleen	Multiple honeycombed abscesses, small patch of severe congestion in right lobe	Mural thrombus in large vein, extending from abscess	
12	70	♀	Cholecystitis (stones) and perforation, general peritonitis, choledocholithiasis	Dilated bile ducts, cholangitis small patches of congestion	Terminal septic thrombi in a medium and in several small veins	Pulmonary infarcts
13	68	♀	Carcinoma of tail of pancreas, metastasis to liver lungs, heart and lymph nodes	Multiple huge carcinomatous nodules	Cancerous and terminal thrombi occluding right main tributary	
14	56	♀	Carcinoma of left ovary, metastasis to liver, peritoneum, kidneys, adrenal glands and lymph nodes	Multiple carcinomatous nodules patchy congestion of right lobe	Organizing laminated and terminal thrombus of right vein, surrounded by cancer	Small pulmonary arteries (emboli) left adrenal vein, both renal veins
15	67	♂	Carcinoma sigmoid, intestinal obstruction	Multiple carcinomatous nodules, patch of congestion (3 cm)	Organizing and terminal thrombi in vein of congested region	
16	74	♂	Carcinoma of bile duct and liver	Multiple carcinomatous nodules, bile ducts dilated right lobe congested	Tumorous and terminal thrombi in most small and medium veins, right lobe	
17	59	♂	Portal cirrhosis, ruptured esophageal varix hemorrhage	Nodular cirrhosis, patchy congestion	Terminal thrombi in many small veins	Lower part of inferior vena cava, both iliac veins
18	46	♀	Duodenal ulcer, general peritonitis	Patch of congestion (5 cm) in right lobe	Organizing and terminal thrombus in medium vein to congested region	
19	59	♀	Ulcerative cholecystitis (stones), perforation general peritonitis	Wedge of congestion (5 cm), atrophic scars	Organizing and terminal thrombi in medium vein to congested region	Inferior vena cava left iliac vein, both iliac arteries, pulmonary emboli
20	24	♀	Chronic ulcerative pulmonary tuberculosis	Wedge of acute passive congestion (1 cm)	Terminal thrombi in small veins of congested region	

of these cases and chronic ulcerative pulmonary tuberculosis in the remaining case In case 19 thrombosis had existed long enough for considerable organization to have occurred

Although asymptomatic thrombosis of the hepatic veins is not important clinically, it is of interest pathologically, as the cause of the condition can be determined in most cases The causative role of inflammatory, neoplastic and cirrhotic processes in the liver as well as of

In dogs complete sudden hepatic obstruction by constriction with a rubber tube causes extreme congestion and enlargement of the liver, ^{17a} the blood pressure drops rapidly, ²² pressure in the

22 Simonds, J P, and Brandes, W W (a) The Effect of Obstruction of the Hepatic Veins on the Systemic Circulation, Am J Physiol 72 320-323 (April) 1925, (b) Anaphylactic Shock and Mechanical Obstruction of the Hepatic Veins in the Dog, J Immunol 13 1-10 (Jan) 1927

portal vein increases^{22a} and the animal may go into shock and die within a few hours^{17b}. The concentration of sugar in the blood drops rapidly,²³ and the animal may die in convulsions^{17a}. The coagulation time is increased greatly. There is a slight decrease in the concentration of plasma fibrinogen and of serum calcium and in the number of blood platelets²³. The concentration of serum lipase may be elevated^{17b}. In human beings, in the few cases of acute, spontaneous occlusion of the liver which have been reported the picture has been similar to that induced experimentally. The picture usually includes premonitory vague epigastric pain, followed by severe abdominal pain⁶ extending to the back, delirium, and, occasionally, vomiting suggestive of acute poisoning¹². Coma may supervene in a few hours⁶. The liver rapidly becomes large and tender, and ascites appears. Severe acidosis with an odor of acetone in the breath, diacetic acid in the urine and increased alveolar carbon dioxide tension may be present²⁴. A diminished value of the plasma cholesterol^{15c} has been noted and attributed to hepatic damage. Death occurs in from twenty-four hours to several days. These profound physiologic alterations are not surprising, because of the extensive destruction of hepatic parenchyma and because of shock. The terminal episode in cases 1 and 4 seems to have been due to acute thrombosis superimposed on a preexisting thrombosis of the hepatic veins.

Thrombosis of the hepatic veins is often chronic. The patient may survive only a few weeks and usually lives less than six months. 1 patient, however, lived twenty-five years⁷. In such patients thrombosis develops slowly or is only partial, as is well illustrated in the 4 cases reported herewith. Evidences of portal obstruction are the outstanding features until acute thrombosis, mesenteric thrombosis or hepatic failure appears.

REPORT OF CASES

CASE 1—History—A white housewife 46 years of age first registered at the Mayo Clinic on Nov 7, 1939, because of swelling of the abdomen. In August 1938, a fibrosarcoma had been removed from the upper part of the shaft of the left femur. In December, pain had developed in the left side of the thorax and the neck and in the left arm, the blood pressure had been found to be lower in the left arm than in the right. In July 1939, pain in the left upper quadrant of the abdomen, a

sensation of abdominal fulness and menorrhagia had developed. In August, total hysterectomy had been performed, at which time a huge leiomyoma had been removed. In September, rapidly progressive abdominal swelling and severe pain in the upper portion of the abdomen had developed. The patient's physician had found that the liver was tender, the liver and the spleen had enlarged rapidly for several days.

Physical Examination—Physical examination at the clinic revealed a pale, chronically ill, apathetic woman. Her temperature was 102 F, the blood pressure in the right arm, in millimeters of mercury, was 129 systolic and 70 diastolic, that in the left arm was 90 systolic and 70 diastolic. The abdomen was moderately distended with fluid. The liver was tender and extended 7 cm below the costal margin. Blood smears revealed hemagglutination. The concentration of hemoglobin was 7.8 Gm per hundred cubic centimeters of blood. The erythrocytes and leukocytes numbered 3,700,000 and 9,100 respectively per cubic millimeter of blood. The serum contained 12.6 Bodansky units of phosphatase per hundred cubic centimeters. Roentgenograms revealed postoperative and inflammatory changes in the left femur.

Course—The patient's temperature rose daily in the afternoon to 100 or 101 F. On November 13 intense pain suddenly developed in the upper portion of the abdomen and in the right lumbar region, followed by vomiting, delirium and shock. The patient died twenty-four hours later.

Autopsy—At necropsy 1,200 cc of ascitic fluid was found in the peritoneal cavity. Each adrenal gland was replaced by a cystic yellow tumor, the right gland weighed 1,000 Gm and the left 850 Gm. Microscopically, these tumors were diagnosed as fibrosarcomas. Growth of the tumors had extended to the inferior vena cava and had obstructed it completely. A terminal thrombus filled the lumen of the inferior vena cava below the tumors. The tumors extended upward into the hepatic veins. Degenerating and terminal thrombi completely occluded the hepatic veins and their tributaries. The liver was purple and congested, it weighed 1,950 Gm and contained multiple metastatic nodules. Sinusoids were distended with erythrocytes, and central necrosis of the lobules was present. The spleen weighed 155 Gm and was normal in appearance. Metastatic lesions were found in the kidneys and the rectal shelf and formed a thrombus occluding the left subclavian artery. Death was attributed to fibrosarcoma of the adrenal glands with extension to the inferior vena cava and the hepatic veins. It was considered that the tumors of the adrenal glands may have been metastatic in origin.

Clinically, the enlarged liver and the ascites indicated involvement of the liver. The history of removal of a fibrosarcoma from the femur a year before the onset of abdominal pain suggested that the process in the abdomen was metastatic. Metastatic carcinoma, particularly of the liver and the peritoneal cavity alone, would have explained the chronic abdominal symptoms and findings. The sudden exacerbation of abdominal pain followed by shock and death within twenty-four hours suggested that rapid progression of the disease had taken place or that some new process had been superimposed on the old one. It is probable that formation of a terminal occluding thrombus of the hepatic venous system and of the inferior vena cava

23 Brandes, W. W. Effect of Mechanical Constriction of Hepatic Veins, with Special Reference to Coagulation of Blood, *Arch Int Med* **44** 676-692 (Nov) 1929.

24 Jacobson, V. C., and Goodpasture, E. W. Occlusion of the Entire Inferior Vena Cava by Hypernephroma, with Thrombosis of the Hepatic Vein and Its Branches, *Arch Int Med* **22** 86-95 (July) 1918.

explains the final picture. The absence of edema of the lower extremities strongly suggests that occlusion of the inferior vena cava did not greatly influence the clinical picture. This case has been reported previously in a presentation in which tumors of the kidney that had involved the inferior vena cava were considered.²⁵

CASE 2—History—A white farmer 56 years of age registered at the clinic on June 16, 1937. In February 1937, he had noted progressive edema of the ankles. At that time he had had an enlarged liver and thrombophlebitis of the right leg. In March 1936, he had had painless massive hematuria for one day. In May 1936, progressive abdominal swelling had developed, abdominal paracentesis had produced 2,000 cc of fluid. Ascites had recurred rapidly. For two weeks before his registration at the clinic he had complained of intense pain in the upper portion of the abdomen and of the lumbar region.

Physical Examination—On physical examination the systolic blood pressure was 170 mm and the diastolic pressure 110 mm of mercury. The abdomen was distended with fluid. Massive edema of the lower extremities was present, extending as high as the lower portion of the abdomen. The liver was enlarged. There was no anemia. The platelets numbered 110,000 and the leukocytes 7,000 per cubic millimeter of blood. The concentration of sodium chloride was 557 mg per hundred cubic centimeters of plasma. The concentration of urea was 44 mg and that of sugar 68 mg per hundred cubic centimeters of blood. The value for bilirubin was 14 mg per hundred cubic centimeters of serum, the van den Bergh reaction was indirect. The bleeding time was increased to six minutes. An examination of blood smears revealed marked macrocytosis of erythrocytes. The results of the sulfobromophthalein sodium test revealed marked impairment of hepatic function. The urine contained a moderate amount of albumin and a few erythrocytes.

Course—Abdominal paracentesis, which was carried out two days after the patient's admission to the hospital, produced 2,100 cc of ascitic fluid. Four days later the patient suddenly went into shock, with cyanosis, dyspnea, failing pulse and coma. The pulse was regular and was not rapid, the cardiac tones were of poor quality. Readings of the blood pressure were low and could not be obtained with accuracy. At this time the leukocytes numbered 17,000 per cubic millimeter of blood. The carbon dioxide-combining power of the plasma was low (34.5 volumes per cent). The patient died eight hours after the onset of shock.

Autopsy—Necropsy disclosed massive edema of the lower extremities. The peritoneal cavity contained only 25 cc of ascitic fluid. The right kidney weighed 745 Gm and was involved by a huge, soft papillary carcinoma, which extended to the right and left renal veins and the inferior vena cava. A laminated thrombus extended down the vena cava into the iliac veins. The tumorous caval thrombotic process extended upward into the right auricle of the heart, through the tricuspid valve and into the right ventricle. Neoplastic thrombosis extended into one of the large hepatic veins of the right lobe of the liver. The other tributary from this lobe was filled with laminated, organized and terminal thrombi. The liver weighed 1,820 Gm and

contained several metastatic nodules. It was moderately congested throughout, blood distended the sinusoids and had caused some central necrosis. There was a wedge-shaped soft, yellowish region about 8 cm in diameter in the left lobe. An organized thrombus obstructed a medium-sized hepatic vein in this region. Several other intrahepatic veins and the common portal vein were filled with organized and recent thrombi. There was chronic passive congestion of the spleen, which weighed 185 Gm. Death was attributed to carcinoma of the right kidney with metastatic invasion of the inferior vena cava, the hepatic veins and the heart.

It is of interest to speculate about the sequence of events in this case. Obstruction of the inferior vena cava was followed by edema of the lower extremities and by thrombophlebitis. Propagation of the tumorous thrombosis into the inferior vena cava above the entrance of the hepatic veins and into the hepatic veins seems to have produced (1) obstruction to the flow of portal blood through the liver, (2) thrombosis of the hepatic veins, (3) congestion of the liver, (4) ascites, and (5) pain in the upper portion of the abdomen and of the lumbar region. Occlusion of the tricuspid valve by the neoplastic thrombus may have been the cause of death, but rapid destruction of the liver may well have played a part. Regardless of the exact sequence of events, however, it is clear that obstruction of the hepatic veins added to the clinical picture. Hepatosplenomegaly and ascites associated with evidence of thrombosis of the inferior vena cava may indicate extension into the hepatic veins, as was suggested by Jacobson and Goodpasture.

In this case and in case 1 thrombosis of the hepatic veins was secondary to thrombosis of the inferior vena cava. In the next 2 cases no satisfactory explanation for the thrombosis could be found in the liver or elsewhere.

CASE 3—History—A white housewife 33 years old registered at the clinic on Nov 18, 1935. Four years previously continuous diarrhea had developed, and the patient had passed each day from five to sixteen stools, which often had contained blood and mucus. She had had abdominal cramps, weakness and slight loss of weight but no fever. Five weeks prior to her registration at the clinic, progressive painless enlargement of the abdomen, with a sensation of bloating, had developed suddenly.

Physical Examination—Physical examination revealed a woman who appeared ill and who had moderate ascites but no edema of the legs. The liver was palpable and smooth. Proctoscopic examination revealed advanced chronic ulcerative colitis, roentgenologic examination disclosed that the entire colon was involved. The concentration of hemoglobin was 106 Gm per hundred cubic centimeters of blood. The concentration of blood urea was 18 mg per hundred cubic centimeters. That of serum protein was 67 Gm per hundred cubic centimeters.

Course—Abdominal paracentesis, which was performed on December 2, produced 1,800 cc of clear, straw-colored fluid, but the ascites recurred rapidly. As the colitis did not improve, ileostomy was performed.

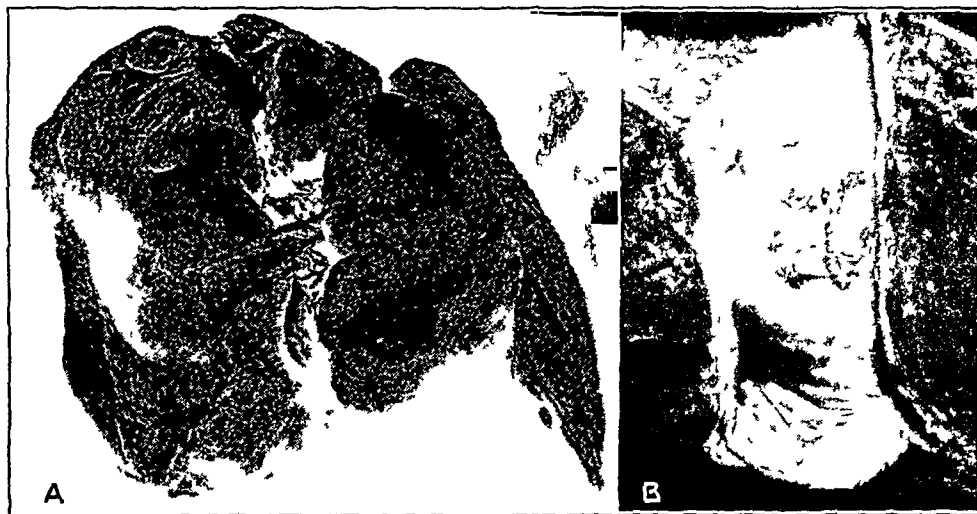
25 Tishch, J. H., Haben, H. C., and Henthorne, J. C. Tumors of the Kidney Which Invade the Inferior Vena Cava. A Report of Seven Cases, Surgery 4: 663-672 (Nov.) 1938.

on December 13 Hepatitis was noted at operation, and 5,000 cc of ascitic fluid was removed. On December 16, pain low in the anterior portion of the thorax, cyanosis, rapid irregular pulse, slight fever and gradual decline developed. The patient became irrational and finally comatose, death occurred on Dec 23, 1935, the terminal temperature was 106 F.

Autopsy—At necropsy the peritoneal cavity contained 3,000 cc of turbid purulent exudate. There were multiple infarcts in the lungs, and the pulmonary arteries contained multiple small emboli. The liver weighed 1,833 Gm. The left lobe was smooth, soft and yellowish, microscopic examination revealed fatty change and slight passive congestion. The right lobe was mottled purple, deeply congested and slightly nodular. Thrombi in the hepatic veins were visible on the cut surface. Some of these were terminal, while others were well organized, with numerous small canaliculi. The walls of the veins were thickened, especially the intima, but there was scant microscopic evidence of inflammation. The main hepatic vein was filled with a terminal thrombus. Patchy central necrosis from passive congestion was present in the right lobe, with some regions of collapse, distortion of lobules and fibrosis but no regeneration. The spleen weighed 138 Gm and appeared

Physical Examination—Physical examination revealed a man who appeared ill and who had moderate ascites but no edema of the legs. The edge of the liver extended 7 cm below the costal margin and was tender. The spleen was palpable. The concentration of hemoglobin was 16.3 Gm per hundred cubic centimeters of blood, the erythrocytes numbered 5,540,000 and the leukocytes 11,500 per cubic millimeter of blood. Blood smears disclosed anisocytosis and increased regeneration of erythrocytes. The concentration of blood urea was 40 mg per hundred cubic centimeters and that of serum bilirubin 2.4 mg per hundred cubic centimeters. The van den Bergh reaction was direct. The sulfobromophthalein test disclosed marked impairment of the function of the liver. The value for serum lipase measured in cubic centimeters of twentieth-normal solution of sodium hydroxide per cubic centimeter of blood was 0.1. A roentgenogram of the stomach did not disclose any abnormality.

Course—Abdominal paracentesis and omentopexy were performed on Jan 3, 1938. Extreme hepatitis was present. Severe pain in the upper part of the abdomen and of the lumbar region continued, and five days after operation delirium, cyanosis, shock and respiratory



A, atrophy of left lobe and hypertrophy of caudate lobe of liver

B, section of inferior vena cava showing ostia of hepatic veins occluded by organized thrombi

normal. Chronic ulcerative colitis was extensive. Death was attributed to chronic ulcerative colitis and general peritonitis.

The possibility that the ascites was attributable to chronic peritonitis must be considered, but this hypothesis seems unlikely in view of the strawlike color of the fluid removed by paracentesis and the absence of gross evidence of peritonitis. The explanation for the ascites in this case was thrombosis of the hepatic veins. An explanation for the thrombosis was not found.

CASE 4—History—A white farmer 41 years old entered the clinic on Dec 30, 1937. Five weeks prior to his registration severe pain in the upper portion of the abdomen and the lower part of the thoracic region had occurred in attacks of five to twenty minutes' duration. The pain had awakened him at night, anorexia and a sensation of fulness after meals had developed. Two weeks later, rapidly increasing swelling of the abdomen had occurred.

irregularity rapidly developed, and the patient died in twenty-four hours.

Autopsy—At necropsy 400 cc of fibrin-flaked fluid was found in the peritoneal cavity. The liver weighed 2,306 Gm. The left lobe was almost completely atrophic. Collapse, fibrosis and distorted lobules were present but hepatic regeneration had not taken place. The right lobe was mottled, dark red and extremely congested, with some patches of atrophy. The sinusoids were distended with conglutinated erythrocytes, which had caused necrosis from pressure of the central two thirds of the lobules. The caudate lobe was unusually large, 14 by 9 by 6 cm, and was congested only slightly (fig. A). Except for two uninvolved accessory tributaries from the caudate lobe, the hepatic veins were filled with old, progressive, organized, canalized thrombi, which extended a short distance into the inferior vena cava as a mural thrombus (fig. B). The walls of the vessels were stenosed and markedly thickened by old fibrous tissue, especially the intima. Only a few inflammatory cells were seen. The lumens were occluded by terminal thrombi which extended down to the central venules. Terminal thrombosis of the intrahepatic portal veins, extending into the common portal,

splenic and mesenteric veins, was present. The jejunum was purplish and hemorrhagic and was the site of venous infarction. The esophageal, retroperitoneal and abdominal veins were extremely dilated. The spleen, involved by chronic passive congestion, weighed 1,103 Gm. Death was attributed to thrombosis of the hepatic and portal veins and infarction of the small intestine.

Case 4 is the most interesting of all those in our series. Only one important pathologic process was present—thrombosis of the hepatic veins. No cause was found for the thrombosis. The effect of the occlusion of the hepatic veins was clearly demonstrated, as it had produced atrophy of the left lobe of the liver and marked enlargement and congestion of the right lobe. The caudate lobe was unaffected but had undergone compensatory hypertrophy (fig 1). Portal hypertension and ascites had followed. The terminal picture followed extension of the thrombus to the portal and mesenteric veins with infarction of the small intestine.

COMMENT

The report of these cases affords an interesting study of the causation, pathologic features and symptoms of thrombosis of the hepatic veins. These cases resemble closely the cases of more chronic thrombosis of the portal vein which have been reported previously in the literature.²⁰ Thrombosis of the hepatic veins secondary to thrombosis of the inferior vena cava is well illustrated in 2 cases (1 and 2), cases 3 and 4 are excellent examples of thrombosis of the hepatic veins for which neither an intrahepatic nor an extrahepatic cause could be found at necropsy. The duration of life in such cases usually is less than six months. The patients in these 4 cases lived five months, five months, nine weeks and five weeks respectively after the onset of symptoms.

The liver usually is large and tender, as it was in these cases, unless cirrhosis was present before the onset of thrombosis. Rapidly progressive hepatic enlargement may be observed, as in case 1. Jaundice has been reported rarely and, when present, has been mild. Visible jaundice was absent in the cases reported, only a slight elevation for the value of serum bilirubin was found in cases 2 and 4. Ascites is an almost constant finding and was present in all 4 cases, paracentesis was necessary in 3. A few cases without ascites have been reported.²¹ The spleen is sometimes enlarged, but this was true only in case 4 of the present series. Edema of the legs in case 2 probably was the result of

associated thrombosis of the inferior vena cava, but it may occur late in the disease as the result of hepatic failure. Increased and even visible collateral circulation of abdominal veins has been reported frequently but was noted in this series only in case 4. Rupture of esophageal varices with gross gastrointestinal hemorrhage has been described.⁶ Acidosis, present before the terminal episode in case 2, has been previously described²⁴ in an instance of acute thrombosis of the hepatic veins. The macrocytosis in case 2 is evidence of hepatic injury.

A significant symptom may be pain in the upper portion of the abdomen and of the lumbar region, which was present in 3 of the 4 cases. The frequency of the occurrence of pain has been commented on by many observers. In cases 1 and 2 lumbar pain may have resulted from the tumor in the renal region, but thrombosis of the hepatic veins was the only explanation for it in case 4. In case 3 neither abdominal nor lumbar pain was a symptom.

Cyanosis was noted during the acute episode in cases 2 and 4 and has been noted not infrequently in other cases. The cyanosis in such cases, as well as the acidosis reported in the case of Jacobson and Goodpasture, is probably part of the picture of shock.

Noticeable in the 4 cases was the tendency of the disease to progress irregularly. The progress was punctuated with sudden development of a new, or exaggeration of an already existent, symptom of the disease, presumably due to extension of the thrombosis.

In case 2 the patient had definite symptoms of pulmonary embolism, and multiple pulmonary emboli were found at necropsy. Portal thrombosis as a result of obstructed circulation existed in cases 2 and 4. Thrombosis of the mesenteric vein with infarction of the small bowel may be the terminal complication, as in case 4.

Pain in the upper portion of the abdomen and of the lumbar region and evidences of disease of the liver and of obstruction to the flow of blood through the portal vein are outstanding features of the more chronic cases of thrombosis of the hepatic veins. The acute episodes are characterized by a sharp exacerbation of the preexisting pain in the upper part of the abdomen, nausea, vomiting, cyanosis, shock with delirium and finally coma and death. Such episodes are well illustrated by the terminal episodes in cases 1 and 4 and possibly in case 2. The terminal acute episodes in cases 1 and 4 lasted twenty-four hours and in case 2 eight hours after the onset of shock.

²⁰ Rolleston and McNee.¹¹ Norman and Allen.^{15b} Osler.¹⁶ McNee, J. W. Croonian Lectures on Liver and Spleen. Their Clinical and Pathological Associations, Brit. M. J. 1 1068-1073 (June 11) 1932.

SUMMARY

Occlusion of the hepatic veins was an incidental finding in 16 of the 20 cases in this series, in the remaining 4 occlusion played a major role in the illness. The occlusion was in all cases due to thrombosis. Although thrombosis of the hepatic veins is a rare condition, it is not so rare that it can be dismissed entirely from the minds of physicians as a diagnostic possibility. In this connection, the 4 cases reported in detail in which thrombosis produced symptoms, were encountered during the six years 1934 to 1939 inclusive.

Occlusion of the hepatic veins may be primary or secondary to inflammatory, cirrhotic and neoplastic diseases of the liver, to thrombosis of the neighboring vena cava, to diseases in which thrombosis occurs frequently, such as polycythemia vera, and perhaps to the slowing of the circulation in debilitating diseases. It may or may not produce recognizable signs and symptoms. It is most often merely an incidental observation at necropsy, but it should be suspected when an acute painful episode with shock occurs during an otherwise chronic course particularly of hepatic disease.

Occlusion of the hepatic veins is of interest not only because of its rarity but also because of the profound physiologic changes which it causes in the liver. These changes are attributable to congestion and atrophy of the liver and to obstruction of the flow of blood through the liver with consequent portal hypertension. In chronic occlusion of the hepatic veins, while acute episodes with shock may punctuate or terminate the course, the mechanical effects of obstruction of the hepatic veins are the well developed features, that is, hepatosplenomegaly, visible collateral circulation and ascites. Thrombosis of the portal vein often occurs, and thrombosis of the mesenteric vein with infarction of the small bowel also may occur. The enlarged, congested liver may become atrophic. In the acute form of the disease and in the acute terminal episodes of the chronic form the more dramatic

features of shock with cyanosis and acidosis are added to those of hepatic and portal obstruction and ascites. Hypoglycemia with hypoglycemic convulsions has been noted experimentally and may be anticipated sooner or later in clinical experience.

In the more chronic forms of the disease the progressive course, in some cases punctuated by acute episodes, the relatively rapid increase in the size of the tender liver and the severe epigastric pain extending to the thoracic or the lumbar region should arouse suspicion that some unusual condition, such as thrombosis of the hepatic veins, rather than cirrhosis or carcinoma of the liver, is the cause of the symptoms. Peritoneoscopic examination may eventually serve to distinguish the congested liver of obstruction of the hepatic veins from the cirrhotic or carcinomatous liver. Hepatosplenomegaly in a case in which evidence of thrombosis of the inferior vena cava has been present will suggest extension of the thrombosis to the hepatic veins. Examination of the direction of the flow of blood in the collateral circulation will aid in the differentiation of obstruction of the hepatic veins and obstruction of the inferior vena cava, as has been pointed out by Thompson and Turnbull among others. An upward flow indicates obstruction of the inferior vena cava, a downward flow, obstruction of the hepatic veins.

In cases of more acute occlusion of the hepatic veins as well as in the acute terminal episodes of the chronic form of the disease the rapidity of increase in the size of the liver together with evidence of profound disturbances of hepatic function and of portal obstruction that could be caused only by some rapidly developing process, such as thrombosis, may well suggest the correct diagnosis. Acute occlusion has been confused with acute pancreatitis, but elevation of values for serum amylase as well as rapid enlargement of the liver and rapid development of portal obstruction should materially aid in distinguishing the two conditions.

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A DENGUE-LIKE FEVER OCCURRING IN IOWA DURING THE POLIOMYELITIS EPIDEMIC OF 1943

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IOWA CITY

During the 1943 epidemic of infantile paralysis, a certain number of patients who were admitted to the isolation division of the University Hospitals with a tentative diagnosis of anterior poliomyelitis proved not to have this disorder. Some of these patients presented the signs and symptoms of an acute illness that could not be classified under any of the known infectious diseases. A review of the literature revealed that a similar syndrome had been described under a variety of names. In an attempt to clear up the confusion of names, we will present a series of cases and a critical review of the literature.

During the months of July, August and September 1943, 10 patients were admitted to the isolation division who presented a not readily classifiable syndrome. A sudden onset of high fever, headache, backache and pains in the limbs typified the course of this acute and rather short-lived disease. The ages ranged between 11 and 20 years, and the average was $15\frac{1}{2}$ years. Eight of these patients were boys, and 2 were girls.

Onset—The onset was characteristically sudden, with high fever, generally preceded by a chill or chilly sensations. Only 1 patient noted an infection of the upper respiratory tract or malaise preceding the rise in temperature. Severe headache, backache and pain in the limbs rapidly ensued and remained the most prominent subjective symptoms. The headaches were located in the frontal and postorbital areas and were accompanied by varying degrees of photophobia. Anorexia and nausea were the rule, and vomiting occurred in 50 per cent of the cases. Two patients noted muscular weakness, and 1 of these also complained of transient sensory disturbances.

Physical Examination—Examination of these patients revealed a surprising paucity of physical signs, and none appeared as ill as his fever would suggest. Three patients showed signs of an infection of the upper respiratory tract at the time of admission to the hospital, but in only 1 of these was it very extensive. A fine maculo-

papular eruption was found over the extremities of 1 patient who had apparently received sulfathiazole previous to his admission. In no instance were cardiovascular or pulmonary abnormalities detected. A mild generalized lymphadenopathy was present in 5 cases, but there was no splenomegaly. Two patients revealed evidences of localized muscular weakness at the time of admission, but none had sensory changes. No instances of pruritus or icterus were seen, and traces of insect bites were lacking.

Laboratory Data—Laboratory studies revealed that the leukocyte counts varied from 3,750 to 15,000, and all but 2 were below 10,000 per cubic millimeter. Of the 5 patients for whom differential counts were made, 4 had over 80 per cent polymorphonuclear leukocytes. Two had mild albuminuria on their entrance to the hospital, but both had normal urine before discharge. A small number of pus cells was noted in the urine of 1 of these patients. Nine patients submitted to lumbar puncture, and all had a normal spinal fluid, including pressure, cell count, protein, sugar, chlorides and Wassermann reaction. Teleroentgenograms were taken of 3 patients, and all were normal. Negative results of blood cultures were found in 5 cases, but in a sixth a hemolytic streptococcus was isolated which, in the light of the future course, was thought to be a contaminant. Agglutination reactions of 7 patients were consistently negative for brucellosis, typhoid and paratyphoid A and B. The Paul-Bunnell test for infectious mononucleosis was given in 2 instances, and an agglutination reaction for tularmia was negative in 1 case. In none of these cases was the Kolmer, Kahn or Kline reaction of the blood positive.

Course and Treatment—No stereotyped form of treatment was followed, particularly in view of the unusual course of the disease. Two patients received sulfadiazine, which apparently had little or no effect. All were treated symptomatically with mild sedatives and analgesics, a soft diet and fluids as they were desired. All but 1 of these 10 patients were entirely well within eight days. Three patients manifested a distinctly biphasic type of illness, with a secondary, less

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severe febrile response within forty-eight hours. In none of these cases was there any definite evidence of postinfection neuasthenia.

REPORT OF CASES

CASE 1—History—The patient was born in 1929 and had suffered no serious illnesses, except for an operation for acute appendicitis in 1938, until the onset of a febrile disease which brought him to the isolation division of the University Hospitals. On arising Aug 15, 1943, he complained of stiffness of his back and all four extremities. By noon of the same day the boy had a severe throbbing headache, located particularly in the frontal region. Although he had no shaking chills or symptoms of an infection of the upper respiratory tract, his temperature was discovered to be 102 F. The following day the patient showed subjective improvement, in that the generalized stiffness had disappeared, although his cephalalgia remained unabated. Moderate chills ensued, and he entered the hospital the afternoon of August 17, with the presumptive diagnosis of poliomyelitis. He denied having stiffness of the neck, muscular weakness or difficulty in breathing and swallowing. Anorexia was present, although the boy had not vomited.

He and a brother 16 years of age had been swimming at Deer Creek two weeks previous to the onset of the illness. This brother entered the hospital on the same date with a remarkably similar group of complaints, also starting on August 15. The patient's parents and two other brothers were well, although the father was reported to be a hemophilic.

Physical Examination—In spite of a temperature of 105 F (rectal) at the time of his admission, the child did not appear acutely ill. He was rational, but rather sluggish, and preferred to lie on his side with his eyes shaded by his arm.

No abnormalities of distribution of hair were noted, his skin was warm and moist, and he had a malar flush but no exanthem. The skull was normal. Hearing and vision were unimpaired, and the external auditory canals and tympanic membranes appeared healthy. A slight nystagmus to extreme gaze in all directions was present, but the pupillary reflexes were active, and the scleras were clear. Ophthalmoscopic examination revealed no abnormalities, but there was mild conjunctival injection. The nasal mucosa was moderately inflamed and showed a serous exudate. The lips were dry and scaly, and the tongue was coated. The teeth, tonsils and pharynx appeared normal except for a mild reddening of the latter. A few pea-sized, discrete, nontender, unattached, rather soft lymph nodes were found in the cervical, axillary and inguinal regions.

The lungs and chest were normal. The heart was not enlarged, but the rate was 100 per minute. A systolic murmur of moderate intensity, which did not entirely disappear on either inspiration or expiration, was heard at the apex. The arterial blood pressure was 110 mm of mercury systolic and 60 diastolic.

The abdomen was scaphoid and showed a well healed scar in the right lower quadrant. The liver and the spleen were not palpable. The genitalia were normal. Inspection of the back revealed mild spasm and tenderness of the lower spinal group of muscles. Pathologic and neurologic signs were wanting.

Laboratory Examination—When the patient was admitted, the hemoglobin content was 11 Gm, and the leukocyte count was 9,000. The urine was normal. Agglutination reactions for brucellosis and typhoid were

negative, as was the heterophile antibody test for infectious mononucleosis. A lumbar puncture on August 17 revealed normal dynamics and a crystal clear fluid with only 2 cells per cubic millimeter. The proteins were 21 mg, chlorides 728 mg and sugar 73 mg, per hundred cubic centimeters, all within normal limits. A culture of the blood showed growth of a member of the bacillus group which the bacteriologist thought was a contaminant. Culture of the spinal fluid showed no growth. The Kolmer, Kline and Kahn reactions were negative.

Summary—There was a history of headache, backache, marked malaise with chilly sensations and biphasic fever, all of short duration, in a boy who revealed amazingly few abnormal physical and laboratory signs. Moderate nasal and posterior pharyngeal injection, mild generalized lymphadenopathy and soreness of muscles of the back were the salient features of the examination.

Diagnosis—This unusual disease, which defied ready classification, was temporarily and colloquially dubbed "Deer Creek fever" or "the swimming disease."

Subsequent Course—With symptomatic therapy alone the temperature, which shortly after the patient's admission reached 106 F, promptly dropped to normal by August 20, only to show a secondary elevation to 101.6 F on August 21 and 22. The degree of fever was an accurate gage of the amount of distress that was experienced. After the patient's temperature returned to normal on August 23, he felt well, and his appetite promptly returned. The mild infection of the upper respiratory tract and lymphadenopathy persisted throughout the illness, but no icterus or exanthem developed. A leukocyte count on August 22 showed 5,000 cells per cubic millimeter. The boy was discharged in excellent condition on August 24.

CASE 2—History—This boy was born in 1924 and suffered no serious illnesses in childhood, although he was subject to generalized headaches. His tonsils were removed uneventfully in 1929 because of repeated sore throat, and he received sulfathiazole internally after being bitten by a dog in May 1943. On the morning of August 20 the patient began to feel weak and dizzy and noted some stiffness in his back and arms. Because of increasing malaise he went to bed a few hours later, complaining of generalized pain in the chest of the pleuritic type. Nausea and vomiting, severe shaking chills and a throbbing frontal headache rapidly ensued, and his temperature rose to 103 F by the evening of the same day. His symptoms continued with unabated intensity (the anorexia was severe), and on August 21 he was given 2 sulfathiazole tablets (0.5 Gm each) every four hours. This medication was discontinued twenty-four hours later, because there was no obvious improvement in the boy's condition. Subsequently he entered the University Hospitals on the afternoon of August 23, with the presumptive diagnosis of infantile paralysis. He denied having a stiff neck, although his back was sore, but he did complain of generalized weakness of his extremities, particularly of the arms.

This patient reported that he had not been in swimming for two months. Except for the fact that his father had headaches, his parents and three siblings had always enjoyed good health, and none was ill at the time with a similar disease.

Physical Examination—This patient had a temperature of 104.8 F on admission but did not appear seriously ill. Some apathy was present, but he had no difficulty in relating his story.

The face was moderately flushed, and the skin was hot and dry. No cranial abnormalities were present.

A thorough examination of the ears and eyes, including otoscopic and ophthalmoscopic studies, was negative in result. The scleras were clear. Moderate injection of the nasal mucosa and enlargement of the inferior turbinates were observed. The lips were dry and the teeth noncarious. The tonsils were absent, but the posterior pharynx showed a moderate reddening and a purulent posterior nasal discharge. Soft, nontender, pea-sized lymph nodes were found in the axillary and inguinal areas.

The thoracic cage, lungs and heart were normal. The arterial blood pressure was 110 systolic and 60 diastolic, and the pulse was regular, with a rate of 104 per minute. No murmurs were present.

The scaphoid abdomen revealed no scars or tenderness, and the spleen and the liver were not enlarged. The genitalia were normal. The musculature of the neck and back was mildly stiff and tender, apparently from spasm. Complete neurologic examination revealed no abnormalities.

Laboratory Examination—When the patient was admitted, there were 4,000,000 erythrocytes and 3,750 leukocytes per cubic millimeter. The urine was normal except for a transient and mild albuminuria. Agglutination occurred with the typhoid “H” antigen at a titer of 1:40 and did not occur with the “O” antigen. Similar reactions for tularemia and brucellosis were negative. A spinal tap on the patient’s first day in the

August. The outbreak was sporadic, the patients all came from five counties of eastern Iowa, with the exception of 1 patient who was sent from the western part of the state. Two of the victims were brothers, and both of these patients were ill at the same time, but there were no known contacts between any of the remaining 8 victims. Contacts with ticks, fleas and mosquitoes were searched for, but no constant history was elicited nor was there a common source of milk, food products or drinking water. However, over half of the patients gave a history of swimming in a creek, lake or swimming pool a short time before the onset of their illness. One victim was found to have drunk water from a well which was thought to have been contaminated.

SURVEY OF LITERATURE

Daniels and Grennan¹ reported a series of 40 cases of an unusual, acute, febrile illness among the soldiers at Fort Bragg, Georgia, during the months of July and August 1942. Nearly all

TABLE 1—Seasonal Incidence by Percentage

Author	Location	Year	March	April	May	June	July	August	Sep tember	Octo ber	Total
Paul, Antes and Sahs	Iowa	1943					30	60	10		100
Grennan and Daniels	Georgia	1942					25	85	12.5		100
Cheney	Northern California	1934		16.7		16.7	33	33			100
Cheney	Northern California	1943-1945			15	10	35	25	10	5	100
Woodland, McDowell and Richards	Texas	1942			100						100
Bowdoin	Georgia	1940						100			100
Topping, Cullyford and Davis	Colorado	1940	6	6	62	22	4				100
Average total			15	2	30	19	8	34	45	1	100

hospital revealed a clear fluid, with normal pressure readings, 2 cells per cubic millimeter and 34 mg of protein, 695 mg of chlorides and 82 mg of sugar per hundred cubic centimeters. No organism was grown from the cultures of the spinal fluid or the blood.

Summary—There was an acute febrile illness, with chills, severe headache and backache in a youth 19 years of age, who showed signs of a minimal infection of the upper respiratory tract, soreness of muscles of the neck and back and a mild lymphadenopathy.

Diagnosis—The illness was diagnosed as an acute infectious disease of unknown cause, but not encephalitis or poliomyelitis.

Subsequent Course—Treatment during his stay of six days in the hospital was nonspecific and symptomatic. Within the first twenty-four hours a moderate, asymptomatic maculopapular eruption developed over the upper and lower extremities and later over his chest and trunk, which was interpreted by the dermatologist as being caused by the administration of sulfathiazole. The fever and symptoms subsided simultaneously, with a temporary exacerbation on August 26 and 27. The exanthem gradually improved, his appetite returned, and the boy was discharged feeling well on August 28.

EPIDEMIOLOGY

Table 1 shows that all 10 patients were seen late in the summer of 1943 and that the majority of the cases occurred during the month of

these patients reported a sudden onset of high fever, followed by severe headache, backache and pains in the extremities. Over half experienced chills, and less than one third showed any symptoms referable to an infection of the upper respiratory tract. About one fourth of the patients suffered from nausea and vomiting. Five of the patients showed a biphasic type of illness, and all were afebrile within eight days.

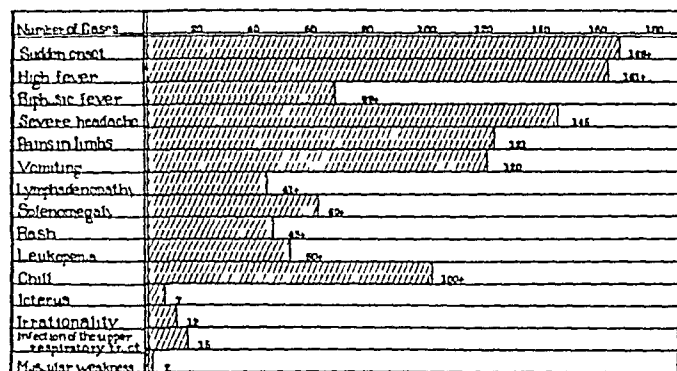
Physical examination revealed few evidences of an infection of the upper respiratory tract. Lymphadenopathy was not remarkable, but 95 per cent showed an enlarged spleen. Thirty-five of the 40 patients had a bilaterally symmetric erythematous, localized blush of irregular outline. In 30 cases the eruption was localized to the pretibial area—whence the title of “pretibial fever.”

A low leukocyte count and relative lymphocytosis were the rule. Cultures of the blood were taken in all cases but showed no growth. Agglutinations were negative for Proteus X₁₀, Brucella melitensis, the typhoid-paratyphoid

1 Daniels, W. B., and Grennan, H. A. Pretibial Fever, J. A. M. A. 122:361 (June 5) 1943.

group and heterophil antibodies, and a search for malarial parasites and the spullum of relapsing fever was unsuccessful. Epidemiologic investigation revealed that all of the patients were quartered in the northern third of the populated area of the reservation, near a small stream and its tributaries. No common insect vectors were found, and there was no evidence that the disease was spread by human contact. A search for the etiologic factor has been started, but no results have been obtained as yet.

Cheney² reported two outbreaks of an acute febrile illness in and around San Francisco during the years 1934 and 1935. As may be noted in the chart, the disease showed a great similarity to the Iowa cases, with sudden onset of high fever, headaches, general malaise and an absence of symptoms of the upper respiratory tract as the salient features. In one third of the 30 reported cases the patient had a nonspecific cutaneous



Incidence of symptoms and findings (composite of all cases)

eruption. The disease was rather short-lived, often with a "camel-back" fever and pronounced postfebrile asthenia. One patient, also suffering from tabes dorsalis with gastric crises, died on the fourth day. The autopsy diagnoses included acute toxic necrosis of the liver, cholelithiasis, arteriosclerosis, bronchopneumonia and syphilitic aortitis. In 4 cases, including the one ending fatally, the disease occurred as the result of inoculation of blood from a patient ill with the disease. The incubation period in these cases was sixty to ninety-six hours. Agglutination studies, blood cultures, Weil-Felix reactions and malarial parasite tests were negative in all cases attempted. A thorough epidemiologic survey revealed no common vectors, except that several of the patients had been bitten by fleas. The dengue-carrying mosquito, *Aedes aegypti*, has not been found in northern California.

2 Cheney, G. Appearance of a Dengue-Like Fever in Northern California, *Arch Int Med* **56** 1067 (Dec) 1935, A Dengue-Like Fever, *California & West Med* **46** 8, 1937.

Woodland and associates³ described in detail an outbreak of Texas tick fever (Bullis fever) which occurred at the Brooke General Hospital, Fort Sam Houston, Texas, during the spring and summer of 1942. The symptoms, physical findings and laboratory studies were unusually similar to those in the Iowa cases. Lymphadenopathy and leukopenia were seen in 33 soldiers, while a nonspecific rash was found in 3. Agglutination determinations for brucellosis, tularemia and the typhoid group were negative. Repeated cultures of the blood and smears were also negative. Six cases were investigated for Q fever, Rocky Mountain spotted fever and typhus by the complement fixation method, and all tests gave negative results. Enlarged lymph glands were examined by biopsy in several cases and disclosed only lymphoid hyperplasia. All patients had been exposed to the bite of the tick, *Amblyomma americanum*, while on duty in the maneuver area at Camp Bullis, Texas, but no positive proof that the tick was the vector was found. All attempts at animal transfer of the disease and at growth of an organism were unsuccessful. Results of inoculations of male guinea pigs with tick emulsions were not conclusive, and wild animals native to the area showed no evidence of the disease.

A similar outbreak in the same area which involved 485 soldiers was reported in the spring of 1943. These cases showed more severe symptoms, and one fatality was reported. This case showed the terminal clinical picture of severe agranulocytic angina and septicemia.⁴

Bowdoin⁵ discussed an outbreak of an unusual syndrome during the month of August 1940, near Wrens, Ga. Thirty-five cases were recognized, but only 17 were studied in any detail. These cases showed a great similarity, in most respects, to the Iowa group of cases. One half of the patients mentioned in this report complained of epigastric pain, and diarrhea was

3 Woodland, J. C., McDowell, M. M., and Richards, J. T. Bullis Fever (Lone Star Fever—Tick Fever). An Endemic Disease Observed at Brooke General Hospital, Fort Sam Houston, Texas, *J. A. M. A.* **122** 1156 (Aug 21) 1943.

4 The rickettsial causation of Texas tick fever has since been proved by studies with guinea pigs (Anigstein, L., and Bader, M. N. Investigations on Rickettsial Diseases in Texas. IV. Experimental Study of Bullis Fever, *Texas Rep Biol & Med* **1** 389, 1943. Livesay, H. R., and Pollard, M. Laboratory Report on a Clinical Syndrome Referred to as Bullis Fever, *Am J Trop Med* **23** 475, 1943). The tick *Amblyomma americanum* has been demonstrated to be a carrier of this disease, which is immunologically different from either Rocky Mountain spotted fever or Q fever.

5 Bowdoin, C. D. A New Disease Entity (?), *J. M. A. Georgia* **31** 437, 1942.

present in 2 patients. A fine, transient, red-dish rash which was most noticeable over the anterior aspects of the legs and which was not unlike measles, was noted in the later cases.

Agglutination determinations which included the typhoid group, brucellosis, endemic murine typhus and tularemia were negative for 11 patients tested. Studies of the blood, cultures of the stools and Weil-Felix tests were consistently negative in results. Interestingly enough, a technician who handled the cultures of the stools acquired the disease in typical form. The only common factor found was that all the patients had been swimming in Brushy Creek within one week of their illness. This creek was known to receive much privy drainage, and it was near a slaughter house dumping grounds.

Topping and others reported⁶ an interesting series of cases of an acute, benign, febrile disease which was apparently caused by the bite of a tick, *Dermacentor andersoni*. This disease, which occurred in Colorado and adjoining states, had been previously described in the literature, but an actual causative agent had not been reported. Topping believed Colorado tick fever to be akin to South African tick fever, Kenya typhus and Columbian spotted fever, all reputedly caused by one of the arthropods, usually a tick. This disease, characterized by fever, headache, backache, muscle pains and photophobia, often shows a "saddle-back" febrile response. Leukopenia is the rule, and an exanthem has not been described.

In the cases reported by Topping the patients were known to have been bitten by the tick *Dermacentor andersoni*, usually within a week of the onset of the illness. Extensive efforts at animal transfer and the isolation of an organism, either from patients or ticks were uniformly unsuccessful.

A survey of a group of unusual illnesses with apparently definite, though still undetermined etiologic factors and with remarkable resemblances in the clinical aspects has been made in detail. A review of the existing clinical entities with known definite etiologic agents shows that many have a surprisingly similar pattern.

Influenza in many respects follows a course quite related to the previously described illnesses. However, as may be seen in table 1, the incidence of the disease discussed here is greatest during the summer months, at which time influenza is relatively uncommon. Because of the fact that the disease has not been transmitted by direct contact with a victim and because of

the too frequent occurrence of a skin eruption and icterus, the diagnosis of influenza is untenable.

The epidemic form of relapsing fever is caused by *Babesia recurrentis*, which is transmitted by the bite of a louse.⁷ This form of the disease is common to Texas and the eastern seaboard states, but it is far more common in Europe and Northern Africa. Various species of soft ticks are responsible for the spread of the nonepidemic form of relapsing fever, a number of rodents serving as intermediate hosts. This form of the disease is prevalent in South and Central America, and a number of cases are reported in the western states, especially California and Texas. The clinical picture is compatible in many respects, the common features being an abrupt onset of high fever, severe headache and body pains. Vomiting and icterus are seen rather commonly, and splenomegaly is the rule. However, signs of an infection of the upper respiratory tract, leukocytosis and a noticeable tendency to febrile relapses tend to differentiate this disease. During the "pretibial fever" outbreak in Georgia in 1942, relapsing fever was seriously considered as a diagnosis, but diligent search of the blood smears failed to reveal the offending spirochete.

The clinical course of Rocky Mountain spotted fever⁸ is generally much more severe, although the onset is surprisingly similar. A high white blood cell count and the appearance of a characteristic rash are almost constant in this well defined disease, which is transmitted by the bite of the tick, *Dermacentor andersoni*, in the Rocky Mountain region, and by the tick, *D. variabilis* in the East and Midwest. The organism, *Dermacentor rickettsii*, usually seen during the summer months, is the causative factor in Rocky Mountain spotted fever.

The epidemic form of typhus,⁹ caused by *Rickettsia prowazekii* and transmitted through the bite of a louse, is usually associated with war and famine and has seldom been seen in the United States. This form of typhus has a strong tendency to run a severe course. The endemic

7 Strong, R. P. Relapsing Fever. *M. Clin. North America* **27** 734, 1943.

8 Topping, N. H. Rocky Mountain Spotted Fever. *M. Clin. North America* **27** 722, 1943. Kelly, F. L. Rocky Mountain Spotted Fever. Its Prevalence and Distribution in Modoc and Lassen Counties, California, Preliminary Report, *California State J. Med.* **14** 407, 1916. Munson, E. L. Rocky Mountain Spotted Fever and Endemic Typhus Fever, *California & West Med.* **41** 365, 1934.

9 Dyer, R. E. Typhus Fever, *M. Clin. North America* **27** 775, 1943. Cumming, J. G., and Senftner, H. F. The Prevention of Endemic Typhus in California. *J. A. M. A.* **69** 98 (July 14) 1917.

6 Topping, N. H., Cullyford, J. S., and Davis, G. E. Colorado Tick Fever. *Pub. Health Rep.* **55** 2224, 1940.

murine form of typhus, most prevalent in the late summer and fall, more nearly approximates the picture of the described outbreaks. This form of the disease is transmitted by the bite of the rat flea. Points where the disease is endemic have been discovered along the entire eastern, northern and western coasts, and as far inland as Cleveland and Cincinnati. Usually this entity presents a typical exanthem starting on the fifth day of the illness, but the eruption may be so transient as to be entirely overlooked. Again, in spite of the infrequency of a low leukocyte count, a high white cell determination is unusual. The consistently negative Weil-Felix reactions and the infrequency of flea bites tend to eliminate the etiologic diagnosis of endemic typhus fever from our series. Brill's disease¹⁰ is believed to be immunologically identical with classic epidemic typhus. Zinnsel feels that this illness has become endemic in immigrant populations, since there is no proof that it is transmitted by the bite of a louse. This disease is most prevalent along the northern coast of the United States and cannot be seriously considered in the diagnosis.

In the United States the mosquito, *Aedes aegypti*, has been found to be the vector for dengue fever,¹¹ which is quite widespread over the tropical and semitropical areas of the world. This disease was first accurately described in this country by Benjamin Rush, who rather aptly referred to the Philadelphia epidemic in the latter part of the eighteenth century as break-bone fever. This clinical entity has been reported in many southern coastal states and as far north as Pennsylvania. The clinical picture has been found to be polymorphic in the various epidemics throughout the world, but the main characteristics were well described by Siler, Hall and Hitchens in 1926. "Typical cases are characterized by sudden onset with physical weakness, headache, postorbital pain and soreness, flushing of the face, suffusion of the eyes, anorexia with loss of the sense of taste, back-

ache, pain in the bones and joints, marked prostration, mental depression and a general feeling of wretchedness. There is a secondary or terminal eruption of a polymorphous character."

The rash, reported by some authors to be present in 80 per cent of their cases, was barely mentioned by Rush. The majority of writers have found a percentage between these two extremes. Leukopenia is the rule, and a biphasic "saddle-back" fever is often seen. Apparently, however, the latter is not too constant a finding. The clinical picture of dengue is thus quite compatible in most respects to the outbreaks outlined in table 2. In fact, it has been stated recently that the "pretibial fever" epidemic in reality was dengue. Cheney seriously considered this disease in his two series of cases but was unable to confirm his suspicions in any manner. No consistent contact with the mosquito *Aedes aegypti*, which carries the virus of dengue in the United States, is present in any of the listed outbreaks.

During the poliomyelitis season these cases will invariably be diagnosed as infantile paralysis. The onset of this condition with a chill speaks against infantile paralysis. Cerebrospinal meningitis is another condition which must be ruled out, as well as acute encephalitis.¹² The absence of any abnormalities in the spinal fluid assists greatly in ruling out the infections of the nervous system which are likely to occur at that time of the year. The severity of the headache was dependent entirely on the height of the temperature and disappeared as the temperature returned to normal.

COMMENT

To try to designate this syndrome by the introduction of another colloquial term would accomplish no useful purpose. Until more specific data are available relative to the cause of this condition, we are content to designate it as a "dengue-like" disorder. The practical implications in recognition of this disorder, however, should not be overlooked. Since these patients became ill during the height of the poliomyelitis epidemic in Iowa in 1943, they were invariably admitted to the isolation division with the tentative diagnosis of early poliomyelitis or meningoencephalitis. As the clinical picture became clearer in our minds, certain features of

10 Holmes, W. H. *Bacillary and Rickettsial Infections*, New York, The Macmillan Company, 1940.

11 Philadelphia in the Summer and Autumn of the Year 1780, Philadelphia, Prichard & Hall, 1789. Rice, L. A Clinical Report of the Galveston Epidemic of 1922, *Am J Trop Med* **3** 73, 1923. Scott, L. C. Dengue Fever in Louisiana, *J A M A* **80** 387 (Feb 10) 1923. Siler, J. F., Hall, M. W., and Hitchens, A. P. Dengue Fever. Its History, Epidemiology, Mechanism of Transmission, Etiology, Clinical Manifestations, Immunity and Prevention, *Philippine J Sc* **29** 1, 1926. Chandler, A. C., and Rice, L. Observations on the Etiology of Dengue Fever, *Am J Trop Med* **3** 233, 1923. Rivers, T. M. Relation of Filtrable Viruses to Diseases of the Nervous System, *Infections of the Central Nervous System*, A Research Nerv & Ment Dis, *Proc* **12** 49, 1932.

12 Toomey, J. A. Differential Diagnosis of Meningeal Irritations, *J Iowa M Soc* **32** 355, 1942. Seiffert, G. *Virus Diseases in Man, Animal and Plant*, New York, F. Hubner Company, 1944. Salzman, S. R. An Infectious Syndrome Resembling Influenza, *Ohio State M J* **38** 328, 1942. *Neurotropic Virus Diseases*. Circular Letter No. 74, Office of the Surgeon General of the Army, *Mil Surgeon* **92** 494, 1943.

TABLE 2—Comparison with Similar Cases Reported

Author	Paul, Antes and Sahs	Grennan and Daniels	Cheney	Cheney	Woodland, McDowell and Richards	Bowdoin	Topping	Total
Diagnosis		Pretibial fever	Dengue like fever	Dengue like fever	Texas tick fever	New disease entity (?)	Colorado tick fever	
Location	Iowa	Georgia	Northern California	Northern California	Texas	Georgia	Colorado	
Year	1943	1942	1934	1934 1935	1942	1940	1940	
Number of cases reported	10	40	10	20	33	17	53	183
	Per Cent of Total							
Sudden onset	90%	100%	100%	75%	Usually	100%	100%	92.5+
High fever	100%	95%	90%	90%	100%		100%	88.5+
Biphasic fever	30%	12.5%	90%	60%	A few		74%	38+
Severe headache	90%	95%	90%	85%	48%	100%	74%	80%
Severe backache	100%	100%	90%	80%	27%	100%	38%	69%
Pains in limbs	100%	100%	80%	70%	42%	100%	32%	68.5%
Vomiting	50%	22.5%	20%	Rare	0%	A large number	10%	22.5%
Lymphadenopathy	Mild 60%	Not remark- able	60%	45%	100%	6		33+
Splenomegaly	0	90%	20%	15%				23.5%
Rash	10% (sulfa thiazole)	87.5%	40%	30%	9%	Six in later cases		30+
Leukopenia	30%	87.5%	40%	60%	100%	All in nor- mal range	In all cases checked	55+
Chill	50%	50%		40%	Usually		57%	52%
Icterus			20%	25%				4%
Irrationality			10%	55%				6.5%
Infection of upper respira- tory tract	Mild 30%	Mild 30%						8% (mild)
Muscular weakness	20% tran- sient							1%
Course	All except 1 well in 8 days	All well in 9 days	One died 4th day, rest well in 16 days, some asthenia	Asthenia for 1 to 2 weeks	Protracted asthenia	Well 7 to 9 days	Afebrile in 7 days, protracted asthenia	
Cultures of the blood	Negative in 1 case, hemolytic str in 5 cases	Negative in 40 cases	Negative in 2 cases		Negative in 33 cases	Negative in 11 cases	Negative in 11 cases	
Agglutination for Brucel- losis, typhoid, paratyphoid, A and B	Negative in 7 cases	Negative in 40 cases	Negative in 2 cases		Negative in 6 cases	Negative in 11 cases		
Smear for malaria		Negative in 40 cases	Negative in 1 case				Negative in 11 cases	
Smear for relapsing fever		Negative in 40 cases					Negative in 11 cases	
Lumbar puncture	Negative in 10 cases	Negative in 3 cases	Negative in 2 cases, in- creased cells and pressure in 1 case	Negative in 4 cases	Negative in several cases		Negative results of cultures	
Heterophil antibody	Negative in 2 cases	Negative in 40 cases			Negative in 2 cases			
Cultures of the stools	Negative in 1 case					Negative in 13 cases		
Agglutination for tularemia	Negative in 1 case				Negative in 6 cases			
Complement fixation for Rocky Mountain spotted fever					Negative in 6 cases			
Complement fixation for Q fever					Negative in 6 cases			
Weil Felix				Negative in 1 case	Negative in 6 cases	Negative in 17 cases	Negative in 11 cases	
Vectors (common)	Five had been in swimming, 1 had drunk contaminated well water	All near same stream	Four re- ceived dis- ease by blood inoculation many bitten by fleas	None found	All bitten by tick A Americ- anum	All were swimming in same creek 1 week before illness	All bitten by tick D Andersoni	
Pathology					Lymphoid hyperplasia (biopsy)			
Etiology		Animal transfer un- successful, no results in studies of local mos- quito and flies			An intracel- lular organism with features similar to those of pathogenic rickettsias		Animal transfer un- successful, no results in tick studies	

the "dengue-like" syndrome established themselves. The onset of the condition with a chill or chilly sensation, the high fever and the lack of true paralysis or alteration in the reflexes tended to rule out poliomyelitis. The only explanation we can offer for the localized weakness presented by several patients is a pseudo-paralysis due to local muscular tenderness. Great reliance was placed on the results of the spinal fluid examination as a means of accurate differentiation from the acute inflammations of the central nervous system and its coverings. The relatively rapid subsidence of symptoms and the absence of sequelae were also important features. The headache and muscular pains are comparable to the symptoms of other severe infections such as smallpox, dengue and typhoid.

SUMMARY

Ten patients were admitted to the isolation division of the University Hospitals with a tentative diagnosis of poliomyelitis. In these patients had developed an acute infectious disease characterized by chills or chilly sensations, severe headache, muscular soreness and high fever. Although the cause is unknown, the condition bears a resemblance to dengue and thus was designated as a "dengue-like" disorder in order not to add another colloquial term to the literature. The differential diagnosis from acute infections of the central nervous system was carefully studied. Undoubtedly, further observation and study of this syndrome may result in the discovery of the etiologic agent, as has been done in the Texas tick fever outbreak.

PRIMARY SPLENIC NEUTROPENIA

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Neutropenia can result from various causes, which include inhibition of granulopoiesis in the bone marrow, arrest of maturation and excessive destruction of neutrophils. It is also a common associated finding in other blood dyscrasias and in some infections and infectious diseases. Neutropenia that arises from depression of bone marrow often is associated with corresponding reduction of other elements formed in the marrow, for example, erythrocytes and platelets. This reduction occurs in the various types of aplastic anemia, in anemia secondary to roentgen and radium irradiation, to exposure to benzene and to the administration of various chemicals, such as derivatives of the benzene ring, arsphenamine, sulfonamide compounds and gold compounds, and in anemia in which the etiologic factor is unknown. The myelophthisic anemias that accompany myeloma, osteosclerosis, Hodgkin's disease, involvement of the marrow by metastatic carcinoma or tuberculosis, leukopenic forms of leukemia and Gaucher's disease often are associated with neutropenia.

In the agranulocytosis of Schultz (malignant neutropenia) profound neutropenia occurs. There may be either pronounced reduction or complete disappearance of granulocytic elements in the marrow, or there may be an arrest of maturation characterized by hyperplastic marrow with increase in the number of young granulocytic forms. Darling, Parker and Jackson¹ termed the latter granulocytic anaknesis. Certain drugs, such as aminopyrine, are common precipitating factors.² The clinical course in the

reported cases was acute, with termination in death or in complete recovery.

Neutropenia commonly is associated with blood dyscrasias such as pernicious anemia and the so-called Banti syndrome. In some specific infections, such as tuberculosis, influenza, malaria, measles and dengue fever, neutropenia frequently is encountered.

Recently Wiseman and Doan³ reported 5 cases in which a syndrome called primary splenic neutropenia was present. The characteristic features were profound granulocytopenia of the peripheral blood, splenomegaly and myeloid hyperplasia of qualitatively normal cells. There was also a characteristic absence of associated hepatic damage such as occurs in Banti's syndrome and of contributing factors such as chronic infection and use of certain drugs, and, finally, there was reestablishment of a normal leukocyte count after splenectomy. The clinical syndrome reported by Wiseman and Doan is thought to be closely allied to thrombopenic purpura and to hemolytic icterus. In primary splenic neutropenia the spleen either destroys neutrophils in excessive numbers or inhibits granulopoiesis in the marrow, while in thrombopenic purpura its action is primarily against platelets, and in hemolytic icterus its action is against erythrocytes. Wiseman and Doan observed some overlapping in the clinical characteristics of the three syndromes. Moore and Bierbaum⁴ and Muether and associates⁵ also

From the Division of Medicine, Mayo Clinic

1 Darling, R. C., Parker, F., Jr., and Jackson, H., Jr. The Pathological Changes in the Bone Marrow in Agranulocytosis, *Am J Path* **12** 1-12 (Jan) 1936

2 Kracke, R. R. Relation of Drug Therapy to Neutropenic States, *J A M A* **111** 1255-1259 (Oct 1) 1938. Madison, F. W., and Squier, T. L. The Etiology of Primary Granulocytopenia (Agranulocytic Angina), *ibid* **102** 755-759 (March 10) 1934. Fitz-Hugh, T., Jr. Sensitivity Reactions of the Blood and Bone Marrow to Certain Drugs, *ibid* **111** 1643-1647 (Oct 29) 1938

3 Wiseman, B. K., and Doan, C. A. A Newly Recognized Granulopenic Syndrome Caused by Excessive Splenic Leukolysis and Successfully Treated by Splenectomy, *J Clin Investigation* **18** 473 (July) 1939. Primary Splenic Neutropenia. A Newly Recognized Syndrome, Closely Related to Congenital Hemolytic Icterus and Essential Thrombocytopenic Purpura, *Ann Int Med* **16** 1097-1117 (June) 1942

4 Moore, C. V., and Bierbaum, O. S. Chronic Neutropenia Treated by Splenectomy, *Internat Clin* **3** 86-95 (Sept) 1939

5 Muether, R. O., Moore, L. T., Stewart, J. R., and Broun, G. O. Chronic Granulocytopenia Caused by Excessive Splenic Lysis of Granulocytes, *J A M A* **116** 2255-2257 (May 17) 1941

reported 2 cases of primary splenic neutropenia

The purpose of this paper is to report an additional case of primary splenic neutropenia. This case presents several unusual features that have not previously been observed.

REPORT OF A CASE

A white woman 60 years of age was first seen by one of us (H M R) on Jan 30, 1942, before she came to the Mayo Clinic. The principal complaints at that time were headache and coryza. There were no symptoms referable to the respiratory, cardiovascular, gastrointestinal or genitourinary system and no history of any type of medication prior to onset of the present illness. The latter statement was confirmed by repeated questioning of the patient and was substantiated by her husband. No chemotherapeutic agents or other drugs that might depress the leukocyte count were administered while the patient was under observation. For approximately ten years the patient

occasional normoblast was present. The results of subsequent studies of the blood are outlined in table 1. The Kahn test of the blood was negative.

The patient's temperature from January 30 to February 5 varied from 100 to 103.4 F (37.8 to 39.1 C). The administration of liver extract, yellow bone marrow extract and a liver-stomach concentrate was started. On February 2, administration of a solution of pentose nucleotide was begun. The dose of pentose nucleotide was 10 cc intramuscularly four times daily for ten days and then once daily for one week. Five hundred cubic centimeters of blood was given on February 4 and 9. On February 4, otitis media on the left side developed and necessitated paracentesis. Slight serous drainage persisted for three weeks. The temperature returned to normal on February 5. The patient remained listless and weak and still complained of moderate exhaustion on dismissal from the hospital on February 16. Subsequent transfusions of 500 cc of whole blood were given on March 24 and April 10. Weakness and exhaustion continued to be prominent symptoms.

TABLE 1—Blood Counts and Values for Hemoglobin Before Operation

Date, 1942	Leuko- cytes, per Cu Mm of Blood	Erythio- cytes, per Cu Mm of Blood	Hemo- globin, per Cent	Leukocytes, per Cent						
				Segmented Polymor- phonuclears	Stab Forms	Juve- niles	Lympho- cytes	Mono- cytes	Baso- phils	Eosino- phils
1/31	1,600			1	7		81	11		
2/ 1		3,750,000	70							
2/ 4	975			2	3		95			
2/ 4	Transfusion of 500 cc of whole blood									
2/ 5	1,190			7	7		76	10		
2/ 6	1,350			11	18		54	14	1	2
2/ 7	2,350			17	28		44	9		
2/ 9	2,650			23	25	2	40	7		3
2/ 9	Transfusion of 500 cc of whole blood									
2/12	4,450	5,050,000	92	27	19	1	40	8		5
2/23	1,950	4,210,000	74	16	4		71	9		
3/ 1	2,050			35	7		50	4		4
3/ 2	2,500			15	5		74	4		2
3/23	975			4	6		78	10		2
3/23	Transfusion of 500 cc of whole blood									
3/26	2,750	4,730,000	80	22	5		65	8		
4/ 8	2,700	4,470,000	77	8	2		81	7		2
4/10	Transfusion of 500 cc of whole blood									
4/10	975	4,520,000	90	3	22		70	44		1
4/23	1,700	4,790,000	74	16	3	3	74	4		
5/10	1,450	4,300,000	76	17	2	1	77	3		
5/25	1,700			12	3	2	82	1		
6/12	1,860			8	4	1	84	2		1
6/22	1,950			18	1	2	75	3		1
8/28	1,500	4,010,000	80	19			61	18	1	1

had known of enlargement of the spleen, which was discovered by her local physician. The history revealed nothing more of significance except the usual childhood diseases and tonsillectomy.

Physical examination showed that the patient was elderly and obese. She appeared to be listless but was not acutely ill. The temperature was 102 F (38.8 C), the pulse rate 80 beats a minute and the respiratory rate 20. The blood pressure was 130 mm of mercury systolic and 80 mm diastolic. Examination of the eyes, nose, throat, chest, heart and extremities gave negative results. There was no evidence of ulceration of the mouth or bleeding of the gums. The abdomen was moderately distended. The spleen was palpable 9 cm below the costal margin. The liver was not palpable.

The concentration of hemoglobin (Sahli) was 70 per cent, erythrocytes numbered 3,750,000 and leukocytes 1,600 in each cubic millimeter of blood. The color index was 0.95. The percentages of the various types of leukocytes were as follows: segmented polymorphonuclears 1, stab forms 7, lymphocytes 81 and monocytes 11. There was slight polychromatophilia, and an

On physical examination in August 1942, when the patient first came to the clinic, there was no essential change from the previous findings. Roentgenologic examinations gave the following results. The chest was normal except for a Ghon tubercle on the right. The esophagus was normal, and there was no evidence of esophageal varices. The stomach also was normal. Examination of blood smears showed relative lymphocytosis, monocytosis, thrombopenia and hypochromic anemia with a tendency to microcytosis of the erythrocytes. No immature myeloid cells were seen. The reticulocyte percentage was 2.7. There was noticeable clot retraction at the end of one hour and complete retraction at the end of two hours. The results of a fragility test, which were normal, were as follows: patient, 0.46 to 0.35 per cent, control, 0.44 to 0.34 per cent. Test of hepatic function by the sulfobromophthalein sodium method showed grade 2+ retention of dye on the basis of a scale of 1 to 4 in which 1 designates the least and 4 the most retention. The concentration of bilirubin was 1.2 mg per hundred cubic centimeters of serum, and the van den Bergh reaction was indirect. The platelets numbered 51,000 per cubic millimeter of blood. Counts

of leukocytes and erythrocytes in bone marrow obtained on sternal aspiration are shown in table 2

TABLE 2—Results of Examination of Bone Marrow Obtained on Sternal Aspiration

Leukocytes	Per Cent	Erythrocytes	Per 100 Cells
Leukoblasts	6	Basophilic normoblasts	2
Neutrophilic		Polychromatic normoblasts	15
Premyelocytes	17	Orthochromatic normoblasts	9
Myelocytes	16	Damaged cells	33
Metamyelocytes	24		
Band forms	10		
Eosinophilic			
Premyelocytes	1		
Myelocytes	3		
Metamyelocytes	1		
Lymphocytes, mature	22		

of the sinuses but no evidence of the fibrosis so commonly seen in Banti's syndrome. Clasmatocytes in increased numbers could not be found. The picture

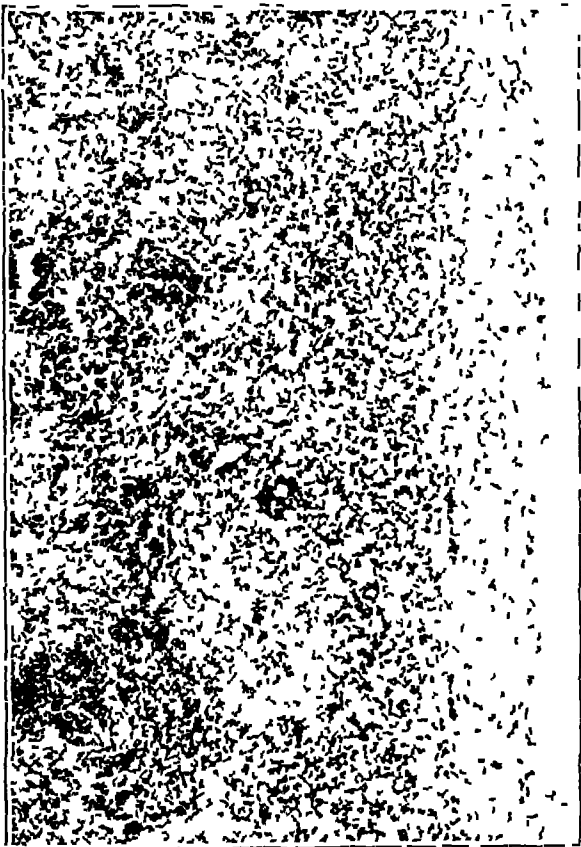


Fig 1—Section of spleen (× 80)

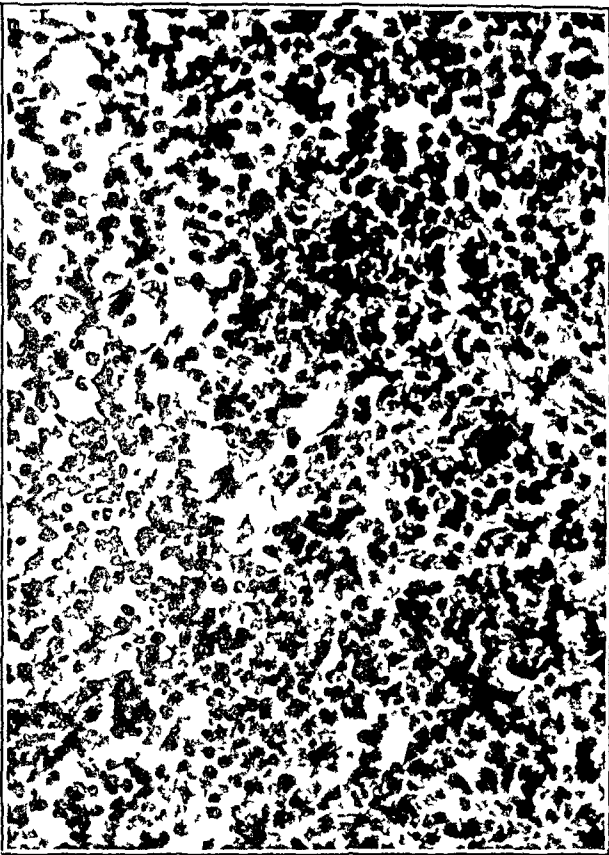


Fig 2—Section of spleen (× 300)



Fig 3—Section of liver (× 80)

The preoperative diagnosis was primary splenic neutropenia, although Banti's syndrome (thrombosis of the splenic vein) could not be eliminated.

On September 4 splenectomy was performed. The spleen weighed 900 Gm. A small ectopic spleen, which was situated retroperitoneally in the region of the upper pole of the left kidney, was found and removed also. Examination of the stomach, duodenum, pancreas and pelvis at operation revealed nothing abnormal. Examination of the liver revealed hepatitis, grade 2 on the basis of a scale of 1 to 4 in which 1 designates the least and 4 the most severe condition. A specimen was removed for study.

Microscopic examination of the spleen showed preservation of architecture. The malpighian corpuscles were normal in number and morphologic appearance (figs 1 and 2). There was an increase in cellularity, but this did not involve the reticuloendothelial elements. The pulp was filled with lymphocytes, erythrocytes and plasma cells. Polymorphonuclear cells were seen but not in increased numbers. There was some dilatation

microscopically suggested chronic splenitis rather than Banti's syndrome. Studies after supravital staining were not done. There was chronic hepatitis with fatty degeneration (fig 3).

Four hours after the operation, the leukocyte count was 7,600 and the erythrocyte count was 3,860,000 per cubic millimeter of blood. Examination of a blood smear revealed microcytosis and signs of increased regeneration of erythrocytes. The following day, numerous neutrophils were seen in the blood smear, and regeneration of erythrocytes was more active. The results of subsequent hematologic studies are recorded in table 3. The postoperative course was complicated by development of atelectasis of the lower lobe of the left lung accompanied by pleural effusion. This subsided spontaneously without the use of chemotherapeutic agents.

During the two years since the operation, the patient's health has been excellent, and the picture with reference to the blood has remained normal. There has been no evidence of hepatic insufficiency. On April 27, 1943, hepatic function as indicated by the sulfobromophthalein method was normal.

operation, there has been no evidence of progressive hepatic disease. On the contrary, the evidence of hepatic damage noted before the operation has disappeared. The fact should be emphasized that hepatitis may occur in primary splenic neutropenia but that this complication, although it increases the risk, does not contraindicate operation and apparently does not decrease the prospect of the ultimate cure.

Wiseman and Doan studied the cells of the splenic parenchyma by means of supravital staining and observed pronounced increase in the number and activity of the macrophages. The macrophages were actively engaged in phagocytosing neutrophils and erythrocytes. While supravital studies were not performed in our

TABLE 3—*Blood Counts and Values for Hemoglobin After Operation*

Date 1942	Leuko- cytes, per Cu Mm of Blood	Erythro- cytes, per Cu Mm of Blood	Platelets, per Cu Mm of Blood	Hemo- globin, per Cent	Leukocytes, per Cent									Reticu- locytes
					Segmented Polymor- phonuclears	Stab Forms	Juve- niles	Lympho- cytes	Mono- cytes	Baso- phils	Eosino- phils	Normo- blasts		
9/ 4	7,600	3,860,000											27	
9/ 5	9,000	2,900,000	209,000		73.5			17.0	9.5			3		
9/ 7	11,000		265,000		80.5			10.5	9.0					
9/ 8	12,500	3,070,000	272,000											
9/ 9	13,200	3,350,000	216,000		87.5			7.5	4.5	0.5		3		
9/10	15,200		348,000		82.5			9.0	8.5					
9/11	9,600	4,060,000			72.5			12.5	14.0	0.5	0.5	2		
9/12	11,500													
9/15	10,800	3,650,000	140,000		81.0			11.5	7.0	0.5				
9/21	10,900		443,000											
9/28	6,500	3,740,000		70										
11/ 6	9,500	5,490,000		85										
1943														
1/ 8	6,400	4,850,000		85										
1/25	9,200	4,890,000		94	39.0	4	2	54.0						
3/26	9,900	4,470,000		85							1.0			
6/25	8,350	4,490,000		85	53.0	12	4	24.0	4.0		3.0		1.0	
12/11	8,100	4,200,000		85	44.0	7	1	46.0	1.0		1.0			
1944														
5/ 4	6,200	4,970,000												

COMMENT

The foregoing case fulfils in general the clinical requirements of the syndrome of primary splenic neutropenia. Profound granulocytopenia, myeloid hyperplasia of bone marrow, splenomegaly and thrombopenia were observed prior to splenectomy. Normal leukocyte and platelet counts were established after operation. The clinical cure by splenectomy of a patient who had pronounced granulocytopenia for eight months should be emphasized. However, in two features, namely, the associated evidence of hepatic disease and the microscopic appearance of the spleen, this case differs from the original cases reported.

The presence of hepatic disease manifested by retention of dye, grade 2, in the sulfobromophthalein test, gross changes in the liver seen at operation and the finding of chronic hepatitis with fatty degeneration on biopsy has not been reported previously in association with primary splenic neutropenia. In the two years since the

case, sections of the spleen revealed no evidence of hyperplasia or phagocytic activity of the reticuloendothelium or of presence of free macrophages in the pulp. This observation agrees with that of Muether and his associates. While the clinical syndrome of primary splenic neutropenia seems well established, the microscopic appearance of the spleen does not seem to be constant.

While other investigators have expressed the opinion that excessive destruction of neutrophils in the spleen is the cause of neutropenia in this syndrome, absence of increased phagocytic activity of the reticuloendothelium in 2 of the 8 cases reported to date raises the question of some other etiologic mechanism. Moore and associates hypothesized concerning the existence of a substance termed a leukolysin, which was formed in the spleen and caused suppressed leukopoiesis in the bone marrow. Although the marrow appeared to be more cellular after splenectomy than it was before, they felt that this change might be due to errors inherent in the technic

of sternal puncture. However, the formation of leukolysin in the presence of this syndrome, in our opinion, has not been disproved.

The differential diagnosis in our case presented some interesting possibilities. Banti's syndrome, or thrombosis of the splenic vein, was seriously considered as a cause of the leukopenia and neutropenia because of the preoperative evidence of hepatic damage. In view of the duration of the splenomegaly and neutropenia, however, esophageal varices and pronounced anemia would probably have been present in association with Banti's disease. Anemia was never a feature of this case, as the erythrocyte count was within normal limits except for those changes that might result from loss of blood at operation. Microscopically, the absence of evidence of hepatic cirrhosis, which might have been expected because of the duration of the disease, and the appearance of the spleen were against a diagnosis of Banti's disease. The improvement after operation, with clinical and laboratory evidence of disappearance of hepatic damage, is further evidence against this syndrome.

Malignant neutropenia was considered but was eliminated by the chronicity of the hematologic findings and the fact that the condition was not precipitated by a drug. Finally, splenomegaly is not an associated finding in malignant neutropenia.

The splenomegaly and neutropenia raised the question of aleukemic leukemia, but the absence of immature forms in the smears of peripheral blood as well as absence of pronounced shift to the left in the bone marrow were sufficient evidence against this diagnosis.

Aplastic anemia was considered in view of the low leukocyte count with depression of granulocytes and associated thrombopenia, but the normal number of erythrocytes and the results of examination of bone marrow eliminated this diagnosis.

SUMMARY

A case that fulfils the clinical criteria of primary splenic neutropenia was observed. This is the eighth case of that disease reported in the literature. The predominating features were profound neutropenia, thrombopenia, splenomegaly and myeloid hyperplasia of bone marrow. Cure was effected by splenectomy. The presence of hepatic damage associated with primary splenic neutropenia is reported for the first time. This complication occurring with primary splenic neutropenia does not contraindicate splenectomy. The details of the microscopic appearance of the spleen in our case varied to some extent from those in the previously reported cases. Primary splenic neutropenia, as well as thrombopenic purpura, congenital hemolytic icterus and Banti's disease (thrombosis of the splenic vein), is a clinical indication for splenectomy.

Progress in Internal Medicine

VASCULAR DISEASES

TENTH ANNUAL REVIEW

THEODORE R VAN DELLEN, M D, GEORGE W SCUPHAM, M D,
GÉZA DE TAKÁTS, M D, AND EDSON FAIRBROTHER FOWLER, M D
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(Concluded from Page 142)

PRIMARY VASCULAR HYPERTENSION

A study of 1 000 normal persons and 272 with hypertension by Amsterdam and Amsterdam⁹⁶ revealed striking differences in systolic blood pressure in the two arms in both groups. The differences were greater in the group with hypertension than in the normal subjects, and the pressure was commonly higher in the right than in the left arm. The differences in diastolic pressure were less pronounced. Age and sex were not factors. Disparities were noted in 76.4 per cent of the normal persons and in 89.3 per cent of those with hypertension. In some cases, particularly in the hypertensive group, the differences were remarkable. This study reveals the importance of making observations on both arms. One side should not be compared to the other, and follow-up observations should always be made on the same side. The causes for such disparity in blood pressure readings lie in the anatomic variations of the main vascular branches of the aortic arch.

An interesting observation has been made by Roth, Robinson and Wilder⁹⁷ on the effect of the cold pressor test on patients with Addison's disease. Some of these apparently show an increased response to the standard cold stimulus. When they were treated with desoxycorticosterone acetate, the blood pressure rose in practically all instances, and in some cases to hypertensive levels. In those in whom the response to the cold pressor test was particularly marked, the maximum and the earliest rise in pressure after treatment were with the drug in question.

96 Amsterdam, B, and Amsterdam, A L. Disparity in Blood Pressures in Both Arms in Normals and Hypertensives and Its Clinical Significance. A Study of 1,000 Normals and 272 Hypertensives, New York State J Med 43 2294 (Dec 1) 1943

97 Roth, G M, Robinson, F J, and Wilder, R M. Changes of Systolic and Diastolic Blood Pressure and the Response of the Blood Pressure to the Cold Pressor Test Among Patients Suffering from Addison's Disease During Treatment with Desoxycorticosterone Acetate, Proc Staff Meet, Mayo Clin 18 450 (Nov 17) 1943

Russek⁹⁸ takes issue with Hines and Brown as to the interpretation of the response to the cold pressor test. He is of the opinion that hyperreaction cannot be regarded as a characteristic of hypertension. He found that there was a definite increase in the number of hyperreactors among older patients. This may be illustrated by the finding that in the 40 to 49 year age group the incidence was 24.2 per cent and that in the 60 to 69 year group it was 56.1 per cent. The average response of both hyporeactors and hyperreactors increased with age, so that he assumed that a person who was a hyporeactor at 40 years might become a hyperreactor when he reached the age of 60. Such an increased response he "attributed to changes in the threshold for pain and increasing vasomotor lability with succeeding decades." The view that a hyperreaction to the cold pressor test is a characteristic of an individual for his lifetime cannot be held in the light of Russek's observations. The hyperresponse of older individuals bears no relation to hypertension, nor is it related to a family history of hypertension.

Observations on blood pressure made by Alam and Smirk⁹⁹ on normal men showed that casual blood pressures, that is blood pressures taken abruptly without preparation, compared with those taken after one-half hour of rest and elimination of emotional reaction to the procedure, were constantly higher. Hypertensive patients with pressures which averaged 195 systolic and 116 diastolic in the casual reading had values of 151 systolic and 95 diastolic under the basal conditions imposed. These findings tend to confirm similar observations reviewed previously. As might be expected, the differ-

98 Russek, H L. The Significance of Vascular Hyperreaction as Measured by the Cold Pressor Test, Am Heart J 26 398 (Sept) 1943

99 Alam, G M, and Smirk, F H. Casual and Basal Blood Pressures. I In British and Egyptian Men, Brit Heart J 5 152 (July) 1943, II In Essential Hypertension, ibid 5 156 (July) 1943. Gatman, M, Amin, M, and Smirk, F H. Casual and Basal Blood Pressures. III In Renal Hypertension, ibid 5 161 (July) 1943

ences between casual and basal blood pressure were much less in cases in which the increased pressure was due to renal disease. The blood vessels in hypertension should be no more reactive to vasomotor stimulation than those of normal persons if the increased blood pressure is due to actual renal disease.

Rogers and Palmer¹⁰⁰ in a discussion of "nervous hypertension" comment on its frequency as noted during physical examination of candidates for the armed forces. In one month, 222 examples of mild transient or variable hypertension were found during the examinations of 1,574 men. The systolic pressure varied from 140 to 160 and the diastolic from 95 to 110, rarely rising as high as 120. About one third had systolic hypertension only.

Such persons with transient nervous hypertension (or casual hypertension) often showed other phenomena of sympathetic stimulation such as tachycardia, sweating and pilomotor reaction. These men also showed a pressor response to cold greater than that observed in normal persons, but less than that in persons with actual mild, early hypertension. The authors are of the opinion that this type of hypertension carries with it an excellent prognosis in regard to both mortality and morbidity. This is based on a follow-up study of 25 cases.

It would seem that the subjects having only an increased systolic pressure must be separated from those having a diastolic rise as well. Those in the latter group, according to most opinion, are candidates for permanent essential hypertension later in life. They might be expected to be hyperreactive to the cold pressor test.

The appearance of acute hypertension has been described as one of the features of acute toxic nephrosis resulting from carbon tetrachloride poisoning.¹⁰¹ It occurs relatively late in the course of the disease, after renal swelling increases the intrarenal pressure. This, Corcoran, Taylor and Pope suggest, results in decreased intrarenal pulsation, which they regard as the most probable mechanism for the production of the renal pressor substance. Hypersensitivity to epinephrine was another feature of this disorder. All symptoms, including the hypertension, disappeared in the case described.

As a result of observations based on the use of spinal anesthesia in patients with hypertension and in normal persons, Gregory, Lindley and

Levine¹⁰² suggest that essential hypertension may have a vasomotor mechanism arising in the central nervous system as well as the generally accepted humoral renal mechanism. The basis of this suggestion was the observation that blood pressure of patients with hypertension fell to relatively low levels during high spinal anesthesia and returned promptly to its former level as the anesthetic action subsided. In persons with normal arterial pressure, there was only a slight fall. Epinephrine had its usual effect on the vasomotor mechanism during anesthesia and at the time blood pressure was found to be lowest.

Page, Taylor, Corcoran and Mueller¹⁰³ described the same procedure, spinal anesthesia to the nipple line, as a means of differentiating what they prefer to label "neurogenic" hypertension from essential hypertension. No consistent change of arterial pressure, renal blood flow or resistance was noted in patients with essential hypertension. In a group of 8 patients with so-called "neurogenic" hypertension, all but 1 showed a fall in arterial pressure. All showed an increase in renal blood flow. They state that such findings point to a participation of a neurogenic vasomotor mechanism in the arterial hypertension of certain patients. They believe that spinal anesthesia offers a means of differentiating the neurogenic from the renal type of essential hypertension.

Page¹⁰⁴ has amplified his views on this subject, and suggests that interruption of vasoconstrictor pathways in patients with so-called "neurogenic" hypertension results in actual renal vasodilatation, while in patients with hypertension of the type in which the renal pressor mechanism is predominant removal of vasoconstrictor impulses has little or no effect.

It would seem reasonable to regard "neurogenic" hypertension not as a separate disease but as an earlier stage of essential hypertension. Certainly there is good reason to believe that in every case of essential hypertension in which the vicious circle of the renal humoral mechanism has been established there must be an inciting stage. This stage is not the same in all cases. Several mechanisms are known, the toxemia of pregnancy

100 Rogers, W. F., and Palmer, R. S. Transient Nervous Hypertension as a Military Risk. Its Relation to Essential Hypertension, *New England J. Med.* **230** 39 (Jan. 13) 1944.

101 Corcoran, A. C., Taylor, R. D., and Page, I. H. Acute Toxic Nephrosis Following Carbon Tetra-Chloride Poisoning, *J. A. M. A.* **123** 81 (Sept. 11) 1943.

102 Gregory, R., Lindley, E. L., and Levine, H. Studies on Hypertension. II. The Effect of Spinal Anesthesia on Blood Pressure of Hypertensive Patients, Its Possible Bearing on the Pathogenesis of Essential Hypertension, *Texas Rep. Biol. & Med.* **1** 167, 1943.

103 Page, I. H., Taylor, R. D., Corcoran, A. C., and Mueller, L. Correlation of Clinical Types with Renal Function in Arterial Hypertension. II. Effect of Spinal Anesthesia, *J. A. M. A.* **124** 736 (March 11) 1944.

104 Page, I. H. Certain Aspects of the Relationship Between Hypertension and Anesthesia, *Anesth. & Analg.* **22** 196 (July-Aug.) 1943.

for one example but probably in most instances the condition is neurogenic in that it is characterized by a vasomotor mechanism which is hypersensitive to stimulation whether that stimulus be cold or emotion. This emotional or neurogenic or psychosomatic hypertension is the "casual hypertension" of Alam and Smirk. All of these terms refer to the same thing, one of the initiating mechanisms of essential hypertension. Attention has been repeatedly called to the temporary rise in blood pressure seen so frequently as a result of the emotional stress of physical examination.¹⁰⁵ The significance of this variability of pressure has not been completely established, but that it is significant in at least some instances of progressive hypertension cannot be doubted, since such variability is seen in sufficient numbers of hypertensive patients to make the impression at least more than suggestive. Apparently, Hines's¹⁰⁶ views are similar.

Friedman and Kasanin¹⁰⁷ studied the renal blood flow and glomerular filtration rate in identical twins, aged 54 at the time of study. One had moderately severe essential hypertension. Blood flow and glomerular filtration were reduced in both. The essential difference in the 2 individuals was in the personality. The patient with hypertension was much more dynamic and energetic than his brother and presented some of the other psychologic characteristics which have been associated with hypertension. From this study, the authors suggest that psychologic factors are important in the genesis of hypertension. It is difficult to draw any other definite conclusion from this paper. One of these twins possessed an inciting factor for his hypertension in his psychologic makeup which was absent in the other.

Trasoff and Schneeberg¹⁰⁸ evaluated the natural concentrations of thiocyanates in the blood of normal human beings. The average levels noted amounted to 1.31 mg per hundred cubic centimeters of blood. They believe that no important factor in the regulation of blood pressure can be ascribed to the normally occurring blood thiocyanates. It is interesting to note that habitual heavy tobacco smokers seemed to have levels well above the average concentration.

¹⁰⁵ Hypertension in Military Service, editorial, *J A M A* **123** 702 (Nov 13) 1943.

¹⁰⁶ Hines, E. A., Jr. Hypertension in Military Service, Correspondence, *J A M A* **124** 667 (March 4) 1944.

¹⁰⁷ Friedman, M., and Kasanin, J. T. Hypertension in Only One of Identical Twins, *Arch Int Med* **72** 767 (Dec) 1943.

¹⁰⁸ Trasoff, A., and Schneeberg, N. G. The Naturally Occurring Blood Sulfocyanates and Their Relation to Blood Pressure, *Am J M Sc* **207** 63 (Jan) 1944.

Golden, Dexter and Weiss¹⁰⁹ have made a most important clinical study of the development and course of the vascular disease initiated by the toxemia of pregnancy, of which hypertension is an essential characteristic. The pattern of this chronic renal vascular disease presents itself in two variations. One is predominantly vascular, with only late manifestations of renal disease which follow the same pattern as essential hypertension, the other, in addition, throughout its course shows considerable evidence of renal disease, with albuminuria, casts and cells in the urine, indicating the presence of glomerular damage much like that of glomerulonephritis. Both forms have the same inciting mechanism, namely, the toxemia of pregnancy. This the authors define as an acute vascular disorder characterized by the appearance in the latter half of pregnancy of an abnormal elevation of blood pressure above the prepregnancy level or an increase in the degree of albuminuria above that existing prior to pregnancy in the absence of other obvious cause. General edema is often associated. These symptoms may diminish before or after delivery. The hypertension may disappear entirely after delivery, as it does in most instances, or it may persist or disappear for a variable latent period and then recur. Albuminuria may or may not accompany the hypertension.

"The most important factor determining the persistence of postpartum hypertension is the duration of the hypertension or the albuminuria during pregnancy no matter how mild it is. Of decidedly secondary importance is the severity of the toxemia." The disorder may exist in a mild or latent phase prior to pregnancy, as indicated by a previous mild elevation of blood pressure, but in the majority of cases in the report the blood pressure was normal either before or in the early stages of pregnancy. The authors indicate that in some instances the prior presence of hypertension is difficult to determine, but that would seem to be of relatively little importance, since the condition is aggravated. In such a case, instead of one, two inciting factors are operating.

The course of the disorder in those cases in which permanent vascular disease develops after toxemia is progressive either slowly or rapidly. In its course, it is identical with essential hypertension. It may increase gradually and slowly, the malignant phase may make its appearance at any time, or may not develop, or the course may be that of malignant nephrosclerosis from the start.

Those cases in which albuminuria was a predominant finding during pregnancy follow a

¹⁰⁹ Golden, A., Dexter, L., and Weiss, S. Vascular Disease Following Toxemia of Pregnancy, *Arch Int Med* **72** 301 (Sept) 1943.

course which resembles more nearly that of glomerulonephritis and may terminate in uremia. The hypertensive form pursues more nearly the course of vascular disease, and is characterized by cerebral vascular accidents and cardiac disease with hypertrophy and failure. In the later stages both types become indistinguishable from their counterparts of glomerulonephritis or essential hypertension both clinically and pathologically. The retinal findings are identical with those of essential hypertension.

The only important difference clinically and pathologically between this and other types of hypertensive renal vascular disease lies in its initiating factor, which here is an acute angiospastic vascular disease, usually of relatively short duration, which terminates after having brought into activity the vicious circle of the renal pressor humoral mechanism with whatever other complicating factors may later intrude themselves in this pattern. A factor of considerable importance is that the inciting mechanism, unless more than one exists, is no longer active. This is not true in the majority of cases of so-called essential hypertension.

Master, Jaffe, Dack and Silver¹¹⁰ in their study of blood pressure in cases of coronary occlusion found a fall in blood pressure in all cases, but in a few the fall was slight. The patients who had hypertension rarely showed a fall below 90, but such a fall was not uncommon in the group with normal arterial pressure. In approximately one fifth of the patients with a previous systolic blood pressure of 200 or more, the blood pressure did not fall below 150. In two thirds of those with hypertension the blood pressure regained an increased level. This took place either promptly or within a year or two.

The mechanism by which such a fall in blood pressure is activated still remains obscure, that it is on the basis of cardiac impairment alone is doubtful. Such a fall in diastolic pressure could not be motivated in this manner.

Further evidence that there is a distinct correlation between the severity of the hypertensive process in man, as indicated by renal clearance studies, and the severity of the vascular disease process, has been shown.¹¹¹ In instances in which there was minimal vascular disease, no impairment in glomerular filtration rate or renal

blood flow could be demonstrated. In cases in which there was advanced vascular disease, both were reduced. The renal clearance remained unaltered after bilateral lumbodorsal sympathectomy except that in 20 per cent of the cases it was temporarily reduced, in some instances for as long as a year. Eventually, however, the blood flow returned to the preoperative level.

Further observations by Foa, Foa and Peet¹¹² on anatomic changes in the vascular system in patients with hypertension are reported. Three hundred and fifty cases in which sympathectomy was done were studied by determination of the ratio of wall to lumen of the arterioles in biopsy specimens of muscle. Those patients whose arterioles showed much thickening of the walls had the more severe symptoms, showed poor therapeutic response and had a high mortality rate. Advanced arteriosclerosis was found to be a bad prognostic indication, and for this reason the writers believe that simple biopsy of muscle is an important factor in determining the severity of the condition in a given case and whether or not the vascular disease process is a reversible one. Only poor results can be expected when there is marked sclerosis of the arteriolar walls. The presence of normal wall to lumen ratios indicates an early form of the disease in which the vasomotor mechanism plays the most important role.

Page¹¹³ and his associates have attempted to learn the identity of the renin activator by electrophoretic studies on the blood serum of the hog. By this process, five distinct proteins were found and it was possible to obtain a globulin fraction which was as effective a renin activator as whole serum. This has been identified as a globulin. They suggest that, instead of calling this substance "renin activator," it be designated as "renin substrate, A₂ globulin." Thus it would appear to be true that renin has the characteristics of an enzyme, which when it acts on this globulin fraction produces "angiotonin" or hypertensine.

Yuile¹¹⁴ has reviewed the reported cases of hypertension associated with pathologic changes in one or both renal arteries. He has classified

112 Foa, P. P., Foa, N. L., and Peet, M. M. Arteriolar Lesions in Hypertension. A Study of 350 Consecutive Cases Treated Surgically, an Estimation of the Prognostic Value of Muscle Biopsy, *J Clin Investigation* **22** 727 (Sept) 1943.

113 Plentl, A. A., Page, I. H., and Davis, W. W. The Nature of the Renin Activator, *J Biol Chem* **147** 143 (Jan) 1943. Page, I. H., Helmer, O. M., Plentl, A. A., Kohlstadt, K. G., and Corcoran, A. C. Suggested Change in Designation of Renin Activator (Hypertensinogen) to Renin Substrate (A₂ Globulin), *Science* **98** 153 (Aug 13) 1943.

114 Yuile, C. L. Obstructive Lesions of the Main Renal Artery in Relation to Hypertension, *Am J M Sc* **207** 394 (March) 1944.

110 Master, A. M., Jaffe, H. L., Dack, S., and Silver, N. Course of Blood Pressure Before, During and After Coronary Occlusion, *Am Heart J* **26** 92 (July) 1943.

111 Talbott, J. H., Castleman, B., Smithwick, R. H., Melville, R. S., and Pecora, L. J. Renal Biopsy Studies Correlated with Renal Clearance Observations in Hypertensive Patients Treated by Radical Sympathectomy, *J Clin Investigation* **22** 387 (May) 1943.

the causative changes as follows 1 Intrinsic factors, such as atherosclerotic plaques, which are present in the majority of instances Thrombosis embolism and congenital defects comprise the remainder of this group 2 Extrinsic factors, including kinking or torsion, aneurysm of the renal artery and extrinsic pressure He concludes that the actual number of reported cases of hypertension associated with "obstructive lesions of one or both main renal arteries in man is not large and in only a small percentage of these can a definite etiologic relation be established between the vascular lesion and the elevation of blood pressure" He feels that too much importance has been given to the coincidence of these two disorders and that no conclusion can be drawn because in most of the instances the combination has been noted in pathologic examination

Richardson¹¹⁵ believes that atheromatous plaques in the main renal arteries may be capable of interfering with the circulation of blood through the kidneys to produce a type of hypertension analogous to experimental hypertension The basis of this opinion lies in pathologic observations at autopsy Twenty-five of 32 patients with hypertension showed the presence of atherosclerotic plaques in one or both renal arteries with some apparent stenosis in each instance Of 113 patients studied at autopsy who did not have hypertension, only 8 showed plaques, and in only 3 were they comparable to those seen in the hypertensive group

In a contribution to the theories in regard to renal blood flow in experimental hypertension, Corrigan and Pines¹¹⁶ conclude that such hypertension depends on the disturbance of balance between the venous pressure and the arterial blood pressure within the kidney When the relative venous pressure is increased, stasis may occur in the renal capillaries and blood flow become short circuited through the arteriovenous shunts As a consequence of this disturbance in blood flow, tissue is deprived of normal blood supply, and the renal pressor substance is then produced They were able to restore the proper arteriovenous pressure balance in their experimental animals, with a consequent reduction of blood pressure Thus they regard as proof that the pressor substance no longer is produced when the venous pressure relationship is restored to normal

115 Richardson, G O Atherosclerosis of the Main Renal Arteries in Essential Hypertension, *J Path & Bact* 55 33 (Jan) 1943

116 Corrigan, F P, and Pines, I Renal Circulation After Compression of the Renal Artery According to Method of Goldblatt Study of the Influence of Renal Venous Runoff on Experimental Hypertension, *Surgery* 14:88 (July) 1943

Braasch and Strom¹¹⁷ have raised the question as to whether or not renal injury may result in abnormal elevation of blood pressure A group of cases was studied, and it seemed that in those cases in which there was secondary infection hypertension was most likely to occur In 3 of 5 cases in which operation (nephrectomy) was done, blood pressure which was elevated returned to normal The authors comment that when hypertension exists following renal injury it is not possible to determine whether the injury is a causal factor in the hypertension unless reasonably accurate records of the patient prior to injury are available

As a result of his review of the literature on the subject and his own experience, Sensenbach¹¹⁸ is of the opinion that unilateral renal disease is only rarely the cause of hypertension Isolated case reports have tended to give this impression, but evaluation of larger groups of cases denies it Furthermore, removal of a kidney which possesses any function at all may be followed by an increase in arterial tension rather than reduction, even though the function of the remaining kidney appears to be normal The age of the patient and the duration of hypertension are important factors in the selection of suitable cases for nephrectomy

This might be explained by the theory that, even though the inciting factor, that is, the diseased kidney, may be removed in such cases, the vicious circle renal mechanism in the other kidney remains effective, further, that arteriolar sclerosis may have reached a degree in the apparently "normal" kidney which has been sufficient to alter renal blood flow Thus it would seem to be important to perform operations of this kind early in the course of disease, before permanent change has taken place in the remaining renal vascular structures

Weiss and Chassis¹¹⁹ report a single case of chronic unilateral pyelonephritis with moderate hypertension of short duration (one and one-half years) Removal of the diseased kidney failed to result in reduction of blood pressure The remaining kidney showed no evidence of disease Effective renal blood flow, glomerular filtration rate and tubular excretory capacity were all increased postoperatively The authors conclude that pyelonephritis in this case had no bearing on the causation of the hypertension

117 Braasch, W F, and Strom, G W Renal Trauma and Its Relation to Hypertension, *J Urol* 50: 543 (Nov) 1943

118 Sensenbach, W Effects of Unilateral Nephrectomy in Treatment of Hypertension, *Arch Int Med* 73 123 (Feb) 1944

119 Weiss, E, and Chassis, H Failure of Nephrectomy to Influence Hypertension in Unilateral Kidney Disease, *J A M A* 123:277 (Oct 2) 1943

Wilhelm and Gross¹²⁰ report an interesting case of the Cushing syndrome, presenting the characteristic features of this condition with blood pressure of 190 systolic and 118 diastolic. The tumor was demonstrated by a special roentgenologic technic. The concentration of urinary estrogen was normal, and the androgen content was greatly elevated, which suggested that the tumor was benign. The neoplasm was removed surgically, blood pressure and other features of the disease returned to normal.

The observations of Warthin and Thomas¹²¹ indicate that hypertension induced by clamping the renal arteries in dogs persists even when renal blood flow is normal. For the first three or four weeks blood flow was reduced, and excretion of phenolphthalein (phenol red) remained well below normal for four to seven weeks, after which it likewise returned to normal. These observations were made on 3 animals with single explanted kidneys. The same conclusion was reached as the result of measurement of the urea clearance in 2 animals with renal hypertension and 2 with neurogenic hypertension. With neither high nor low protein intake was there any effect on arterial pressure which could be regarded as sufficiently great to be important.¹²² The same conclusions were reached when the same animals were used to study the inulin and diodrast clearances.¹²³ Blood flow and renal function remained unimpaired. The response to increase in the protein intake was the same as it was in normal animals.

It has been possible to produce experimental chronic hypertension in dogs by intermittently ligating the arteries supplying the head.¹²⁴ Removal of the carotid sinus had no lasting effect on blood pressure, nor was manipulation effective in altering it.

120 Wilhelm, S. F., and Gross, S. Surgical Removal of Adrenal Adenoma with Relief of Cushing Syndrome, *Am J M Sc* **207** 196 (Feb) 1944.

121 Warthin, T. A., and Thomas, C. B. Studies in Experimental Hypertension. I Phenol Red Excretion and Renal Blood Flow in Hypertension of Renal Origin, *Bull Johns Hopkins Hosp* **72** 203 (April) 1943.

122 Alpert, L. K., and Thomas, C. B. Studies on Experimental Hypertension. II The Effect of Dietary Protein on the Urea Clearance and Arterial Blood Pressure in Chronic Hypertension, *Bull Johns Hopkins Hosp* **72** 274 (May) 1943.

123 Alpert, L. K., and Lilienthal, J. L., Jr. Studies in Experimental Hypertension. III The Effect of Dietary Protein on the Clearances of Diodrast and Inulin by the Kidney in Chronic Hypertension, *Bull Johns Hopkins Hosp* **72** 286 (May) 1943.

124 Fishback, H. R., Dutra, F. R., and MacCamy, E. T. Production of Chronic Hypertension in Dogs by Progressive Ligation of Arteries Supplying the Head, *J Lab & Clin Med* **28** 1187 (July) 1943.

Cromartie¹²⁵ has described an inflammatory disease of rats in which there was a general arteritis of a type which pathologically resembled periarteritis nodosa in man. This was induced by application of layers of cotton cloth to the surfaces of one or both kidneys. In some instances, perinephritis developed with arterial hypertension, in some, only hypertension, and in others, only suppurative disease of one or both kidneys.

After prolonged feeding of a diet deficient in the heat-stable fractions of the vitamin B complex, hypertension is induced in rats.¹²⁶ Associated abnormal phenomena are found in the kidneys of such animals. The surface becomes granular. The afferent arterioles of the glomeruli show subendothelial hyaline deposits which encroach on the lumen. The interlobular arteries show the same changes, and in addition degeneration of the media occurs. Circulation is also impaired. The glomeruli are reduced in size, and the basement membrane is thickened. In some respects these lesions are similar to those seen in the kidneys of human beings with hypertension.

Selye and his associates¹²⁷ were able to produce nephrosclerosis with arterial hypertension in rats by the administration of an overdose of desoxycorticosterone acetate, particularly if a high intake of sodium chloride was maintained. Rather severe edema developed in these animals, and cardiac failure was a frequent cause of death. The pathologic pattern was similar to that of malignant nephrosclerosis, with hyaline and necrotic degeneration of the arteriolar walls.

The medical treatment of essential hypertension has made no progress in the past year. The status of thiocyanate therapy remains the same. Toxic effects and complications of its use are the most important contributions. The promise of depressor renal extracts continues unfulfilled. The chief hope lies in a better understanding of the inciting mechanisms, and surgical treatment at the present time offers the most benefit in actual control of the disease. The many and widely different nostrums are proof, to paraphrase an old adage, that when no specific treatment exists there are a thousand cures.

Kapernick¹²⁸ found no particular value for the reduction of blood pressure in hypertension in the use of such drugs as theobromine, theobro-

125 Cromartie, W. J. Arteritis in Rats with Experimental Renal Hypertension, *Am J M Sc* **206** 66 (July) 1943.

126 Calder, R. M. The Renal Pathology of Nutritional Hypertension in Rats, *J Exper Med* **79** 215 (Feb) 1944.

127 Selye, H., Hall, C. E., and Rowley, E. M. Malignant Hypertension Produced by Treatment with Desoxycorticosterone Acetate and Sodium Chloride, *Canad M A J* **49** 88 (Aug) 1943.

128 Kapernick, J. S. The Blood Pressure in Essential Hypertension. Effect of Several Reputedly Hypotensive Drugs, *Am Heart J* **26** 610 (Nov) 1943.

mine and phenobarbital sodium, tocapral, theophylline ethylenediamine, phenobarbital, cythinitol tetramtrate, hepvise and allimin.¹²⁹ According to his observations, no depression of blood pressure can be expected from their use.

Forster¹³⁰ has reviewed the use of sodium or potassium thiocyanate in the treatment of hypertension. This paper includes, briefly, the most important contributions on the subject, including the pharmacodynamic effects, toxic actions and clinical use of these drugs. He concludes that the majority of clinical workers believe thiocyanates have a definite effect in the reduction of elevated blood pressure, but that this has not been demonstrated experimentally. It is emphasized that drugs of this kind are not a cure for hypertension and that relief of subjective symptoms bears a minimal relation to the fall in blood pressure secured.

In 20 patients with hypertension treated with vitamin A, Blumenthal and Wetherby¹³¹ found no improvement. In 70 patients treated coincidentally with potassium thiocyanate controlled by determination of blood values, symptomatic relief was secured in 43 and some reduction in pressure in the majority.

Further evidence for caution in the use of potassium thiocyanate in the treatment of hypertension is shown by the reports of acute goiter developing during the course of treatment.¹³² Such instances have not been uncommon. The goiter is often large, makes its appearance suddenly, and may be painful, usually because of the rapid increase in size.

The pathologic picture is not that of exophthalmic goiter, and there were no clinical evidences of thyrotoxicosis. As has been shown before, this type of goiter seems to be characteristic.

The description of thiocyanate-induced goiter by Rawson, Hertz and Means¹³³ includes enlarg-

ment of the thyroid gland, symptoms of hypothyroidism with low basal metabolism, often exophthalmos and decreased excretion of the thyrotropic hormone in the urine, in the inactivated form. Low concentration of iodine in the blood was also noted. Apparently, the appearance of this type of goiter can be prevented by the assurance that the patient has had previously an adequate amount of iodine, and after the goiter has developed it can be controlled by the proper administration of thyroid. This particular paper is important because of the intensive study made and its relation to the problem of the pathogenesis of goiter.

Koffler and Freireich¹³⁴ have reported 4 cases of thrombophlebitis in patients treated with potassium thiocyanate. They were not able to demonstrate any other cause and concluded that this disorder must be a complication resulting from a toxic effect of thiocyanate.

Taylor and his associates¹³⁵ studied the effect of vitamin A concentrates given in amounts of 100,000 to 400,000 U. S. P. units daily for from five to ninety days in 2 persons with normal blood pressure and 14 with hypertension. No alteration in the blood pressure levels were noted in any of the cases studied. It was found that as a result of studies of urea, diodrast and inulin clearance renal vasodilatation did occur, and with it increased functional secretion of diodrast along with increased cardiac output.

In contrast is the report of Govea¹³⁶. Almost 50 per cent of 420 patients with hypertension treated with massive doses of vitamin A showed a significant reduction of blood pressure. There was improvement in subjective symptoms, particularly headache. Both oral and parenteral routes for the administration of the drug were employed. Govea Peña and Ibarra also are of the opinion that the effect of this therapy is on the renal parenchyma, with an increase in the rate of renal blood flow. Hypertension which does not respond is thought to be of extrarenal origin.

Pond and Rosen¹³⁷ also report success in the use of vitamin A. Of the cases treated, they report a gradual fall in blood pressure in 10 over

129 Tocapral (Winthrop Chemical Company, New York) contains theobromine, N-methylethylphenyl barbituric acid and calcium iodide diethanolamine. Hepvise (E. Fougera and Company, Inc., New York) is a combination of viscum album extract, desiccated liver and desiccated pancreas. Allimin (Van Patten Pharmaceutical Company, Chicago) contains dehydrated root bulbs of garlic and dehydrated parsley shoots.

130 Forster, R. E., II. The Medical Use of Thiocyanates in the Treatment of Arterial Hypertension, *Am J M Sc* **206** 668 (Nov.) 1943.

131 Blumenthal, J. S., and Wetherby, M. Potassium Thiocyanate in Hypertension, *Minnesota Med* **27** 177 (March) 1944.

132 Potter, E. B. Acute Goiter Due to Cyanate Therapy. Report of Two Cases with Thyroidectomy, *J A M A* **124** 568 (Feb 26) 1944. Foulger, M. P. H., and Rose, E. Acute Goiter During Thiocyanate Therapy for Hypertension, *ibid* **122** 1072 (Aug 14) 1943.

133 Rawson, R. W., Hertz, S., and Means, J. H. Thiocyanate Goiter in Man, *Ann Int Med* **19** 829 (Dec.) 1943.

134 Koffler, A., and Freireich, A. W. Thrombophlebitis as a Hitherto Unreported Complication of Thiocyanate Therapy in Hypertension, *Am J M Sc* **207** 374 (March) 1944.

135 Taylor, R. D., Corcoran, A. C., Shrader, J. C., Young, W. C., and Page, J. H. Effects of Large Doses of Vitamin A Concentrate on Normal and Hypertensive Patients, *Am J M Sc* **206** 659 (Nov.) 1943.

136 Govea Peña, J., and Ibarra, J. Vitamin A and Arterial Hypertension. Mechanism of the Hypoactive Action of Vitamin A, *Rev cubana de cardiol* **4** 116 (April-June) 1943.

137 Pond, A., and Rosen, A. M. Preliminary Report on the Clinical Use of Vitamin A in the Treatment of Hypertension, *Rocky Mountain M J* **41** 242 (April) 1944.

a prolonged period. They suggest that the depressor effect may be associated with the increase in renal function or that some substance present in the compound may be responsible for its action on blood pressure.

Katz, Rodbard and Meyer¹³⁸ studied the effect of vitamins A and D on dogs with experimental hypertension. They were unable to show that vitamin A in large doses was capable of lowering the blood pressure in these animals. Vitamin D failed to elevate the blood pressure in normal dogs. Only occasionally were slight variations noted when these substances were administered in doses sufficiently large to be effective.

Testosterone has been added to the number of drugs for which some value has been claimed in controlling high blood pressure. Márquez¹³⁹ reports definite improvement in the subjective symptoms (as with many other drugs) as well as reduction of the arterial pressure. He emphasizes the use of adequate doses. Favorable results began to appear only after 50 to 89 mg had been injected.

Flaxman¹⁴⁰ compared the mortality figures for 350 patients with hypertension treated surgically, as reported by Max Peet and his co-workers, with those for 244 patients treated symptomatically in his own observation. There was no essential difference in the mortality of the two groups. He believes that it is doubtful whether surgical treatment can alter the course or prognosis of the disease.

VASCULAR SURGERY

BY DR. DE TAKATS AND DR. FOWLER

Vascular surgery is obviously focused this year on war injuries and their sequelae, of the large volume of contributions only a few representative articles have been selected, next in line is the interest in venous ligations undertaken to prevent and treat pulmonary embolism.

VENOUS THROMBOSIS AND EMBOLISM

Thrombosis of the axillary vein due to strain in Navy personnel is reported in two separate articles¹⁴¹. This well defined lesion occurs overwhelmingly in young, healthy males, always on the right side, unless the patient is left handed.

138 Katz, L. N., Rodbard, S., and Meyer, J. Blood Pressure Responses of Dogs to Vitamin A and Vitamin D₂, *Am J Physiol* **140** 226 (Nov.) 1943.

139 Márquez, A. L. Influence of Testosterone on Hypertension in Men, *Semana med* **1** 1180 (May 27) 1943.

140 Flaxman, N. Treatment of Hypertension. Comparison of Mortality in Medically and Surgically Treated Cases, *Ann Int Med* **20** 120 (Jan.) 1944.

141 (a) Stabins, S. J. Primary Thrombosis of the Axillary Vein Due to Strain, *U S Nav M Bull* **41** 1106 (July) 1943. (b) Willcutts, M. D., and Shelburne, S. A. Thrombosis of the Axillary Vein, *ibid* **41** 1730 (Nov.) 1943.

Phlebography and determinations of circulation time and venous pressure are the recommended diagnostic procedures. Stabins^{141a} recommends conservative management followed later by resection of the thrombosed segment. Neither of the articles stresses the early use of paravertebral block, which accelerates the disappearance of the edema, or of anticoagulants, which limit the clot to the traumatized venous segment.

Allen and his co-workers¹⁴² state that interruption of the femoral vein for the prevention of pulmonary embolism is a simple, safe procedure which even very ill patients can tolerate. The operation should be carried out not only after a pulmonary infarct but when thrombosis of deep veins is diagnosed or suspected. Phlebograms are misleading. The authors advocate bilateral venous interruption, especially in patients over 40 years of age. The common femoral vein is exposed, and if it contains a thrombus this is aspirated through a drinking tube. Should no thrombus be present, the superficial femoral vein can be tied, the deep femoral vein and the saphenous veins being left for collaterals. Patients treated in this way have little postoperative edema. They may have to wrap their legs for a few weeks.

The problem has not seemed so simple in our experience. Many patients arrive at the hospital a week or two after the thrombus has reached the groin. Sucking out the organizing thrombus seems unnecessary at this stage. Ligation of the superficial femoral vein may lead to fatal pulmonary embolism from the deep femoral vein, as in the case of Whiting,¹⁴³ who even used anticoagulants, although obviously not in sufficient doses. Then, again, in at least half of the patients permanent edema develops or there may even be recurrent attacks of superficial phlebitis in the extremities whose femoral veins have been ligated. The indication is clearcut for patients who have had a pulmonary infarct and in whom the thrombus can be localized in the deep veins of the lower leg by physical signs or occasionally by phlebography.

Homans¹⁴⁴ in an article on thrombosis of the quiet type (phlebothrombosis) emphasizes the

142 Allen, A. W., Linton, R. R., and Donaldson, G. A. Thrombosis and Embolism. Review of Two Hundred and Two Cases Treated by Femoral Vein Interruption, *Ann Surg* **118** 728 (Oct.) 1943.

143 Whiting, L. W. Postpartum Pulmonary Embolism. The Problem of Femoral Vein Ligation as a Prophylactic Measure, *Ohio State M J* **39** 1027 (Nov.) 1943.

144 Homans, J. Deep Quiet Venous Thrombosis in the Lower Limb. Preferred Levels for Interruption of Veins, Iliac Section or Ligation, *Surg, Gynec & Obst* **79** 70 (July) 1944.

importance of detecting an early stage of this progressive disease when the process is still confined to the lower part of the leg or has given rise to an unattached floating thrombus in the femoral vein, threatening pulmonary embolism. The indication is clear for an interruption of circulation in the femoral vein to forestall not only embolism but the development of a typical iliofemoral thrombosis (milk leg). But he also discusses a more advanced stage of thrombosis, more or less adherent but not obstructive, which has propagated above the inguinal ligament into the external and occasionally, especially on the left side, into the common iliac vein. Such a process may be associated with thrombosis of the deep veins of the thigh draining through the deep femoral vein. The advantages of ligating the common iliac veins and not the common femoral veins is thoroughly discussed. Also some observations are made on the interruption of the vena cava. This is a significant article, and its careful study is highly recommended.

Atlas¹⁴⁵ reports a thrombosis of the inferior vena cava following amputation. The vein was tied just below the renal vein. The edema promptly disappeared. There are a considerable number of patients suffering from occlusion of the inferior vena cava with collateral veins in the abdomen and frequent ulcerations of the leg. Should they all have a ligation proximal to the thrombus? This question is intriguing and awaits an answer.

A gunshot wound so damaged the superior mesenteric vein of a patient that it had to be ligated¹⁴⁶. The mortality rate of spontaneous occlusion of the superior mesenteric vein is about 100 per cent. Postoperatively this patient had early adequate heparinization and the blood pressure, blood volume and oxygenation of tissues were maintained to aid in the development of adequate collateral circulation. A second operation, done for duodenal obstruction, revealed dilatation of the superior and inferior pancreaticoduodenal and gastroduodenal veins, which served as collateral channels. Anastomosis between the middle and left colic veins assisted the venous return from the ascending and transverse colon.

ARTERIAL OCCLUSIONS

An interesting experimental study on the prevention of gangrene following ligation of major arteries has been presented by Spiegel, Fried-

lander and Silbert¹⁴⁷. They pumped blood from the abdominal veins into the femoral artery of dogs whose femoral artery was ligated proximal to the anastomosis. Anticoagulants were used to prevent gangrene in several of the animals. In its present form the method is hardly applicable to human beings.

An excellent review of the treatment of peripheral arterial embolism is given by McClure and Harkins¹⁴⁸. They collected a series of reports of 690 peripheral arterial embolectomies and report 10 of their own. Twenty-one successful aortic embolectomies are reviewed. This contribution does not lend itself to a brief abstract, but it emphasizes the limitations, indications and results of embolectomy. Duncan and Myers¹⁴⁹ and Agar¹⁵⁰ give a gist of the accepted indications for and technic of embolectomy, they emphasize early diagnosis and early surgical therapy as the method of choice.

Five aortic embolectomies are described by Murray,¹⁵¹ who uses an extraperitoneal approach, and one by Winkle and Cabot¹⁵². It is apparent from these case histories that the real problem after restoration of the occluded circulation is to prevent further emboli, which often vitiate the early brilliant results. Anticoagulants, as used at present, have not entirely solved this problem.

Wetherell¹⁵³ suggests a practical, three phase division of the treatment of arterial embolism. During the first phase the site of the embolus is located and $\frac{1}{2}$ to 2 grains (0.03 to 0.12 Gm.) of papaverine hydrochloride is given intravenously. If the improvement is questionable he proceeds with anticoagulants and uses a paravertebral sympathetic block. Should this fail he does an embolectomy with the area under local anesthesia and continues anticoagulant therapy.

Patients with acute arterial occlusions should certainly be hospitalized with alacrity. The first physician should administer papaverine. It is less generally known that the early use of heparin

147 Spiegel, R., Friedlander, M., and Silbert, S. The Prevention of Gangrene Following Ligation of Major Arteries—Experimental Study, *Surg., Gynec. & Obst.* **77** 162 (Aug.) 1943.

148 McClure, R. D., and Harkins, H. N. Recent Advances in the Treatment of Peripheral Arterial Embolism, *Surgery* **14** 747 (Nov.) 1943.

149 Duncan, R. D., and Myers, M. E. Peripheral Arterial Embolism, *Am. J. Surg.* **62** 34 (Oct.) 1943.

150 Agar, H. Peripheral Arterial Embolism, *Brit. M. J.* **2** 101 (July 24) 1943.

151 Murray, G. Aortic Embolectomy, *Surg., Gynec. & Obst.* **77** 157 (Aug.) 1943.

152 Winkle, H. T., and Cabot, N. Embolectomy for Riding Embolus of the Abdominal Aorta, *Surgery* **13** 264 (Feb.) 1943.

153 Wetherell, F. S. The Treatment of Arterial Embolism of the Extremities—A Three-Phase Division, *New York State J. Med.* **44** 35 (Jan. 1) 1944.

145 Atlas, L. N. Ligation of the Inferior Vena Cava, *Ohio State M. J.* **39** 917 (Oct.) 1943.

146 Schnug, E. Ligation of the Superior Mesenteric Vein, *Surgery* **14** 610 (Oct.) 1943.

is of great value, since it inhibits propagation of the thrombus. This regimen in our experience has saved a number of extremities, with or without embolectomy. Even the most successful embolectomy cannot remove a massive descending thrombosis extending from the groin to the foot.

Learmonth and his associates¹⁵⁴ report 4 cases of localized arterial thrombosis in otherwise normal adults. They believe trauma is the likeliest predisposing cause. They advocate preganglionic sympathectomy or arteriectomy for relief of pain and improvement of circulation. Injury seems to have been the immediate cause for arterial occlusion in the hands and feet of patients exposed to repeated occupational trauma in 11 cases described by Barker and Hines¹⁵⁵. The average age of these patients was 46, and they did not have arteriosclerosis, cervical rib, scalenus anticus syndrome or evidence of occlusive arterial disease elsewhere.

Such cases are not too infrequent in vascular clinics. A case of an osteopath whose massaging fingers showed digital thrombosis comes to mind. He was greatly benefited by a preganglionic sympathectomy.

ANEURYSMS AND OTHER VASCULAR INJURIES

Gage¹⁵⁶ reemphasizes the simplicity and practical value of the Matas endoaneurysmorrhaphy in the saccular and fusiform types of aneurysm. Preoperatively the adequacy of collateral circulation must be tested either by temporary compression of the vessel or by sympathetic block. Cases of traumatic arteriovenous fistula are reported by Wise¹⁵⁷ and Penick¹⁵⁸. Excision of the fistula with quadruple ligation is recommended. A study of 67 peripheral aneurysms and arteriovenous fistulas has been made by Pemberton and Black¹⁵⁹. For arterial aneurysms excision of the sac is recommended, whereas for arteriovenous fistulas quadruple ligation with ex-

cision of the sac is the method of choice, sometimes simple ligation of the communication between artery and vein may prove satisfactory.

Watson and Miller¹⁶⁰ present a case of extreme dilatation of the external iliac vein in an arteriovenous fistula affecting the femoral vessels. They describe the physiologic changes accompanying an arteriovenous fistula and the difficulties encountered in the surgical repair of the fistula.

Other traumatic aneurysms are reported by Langley¹⁶¹ and Handley and Oldfield¹⁶². Such reports emphasize the necessity of special training in handling difficult vascular problems. The successful use of a cellophane cuff to obliterate a subclavian aneurysm slowly is reported by Harrison and Chandy¹⁶³.

The difficulties of ligating the abdominal aorta for aneurysm are graphically described by Morton and Scott¹⁶⁴. In their case the aneurysm had developed just below the origin of the inferior mesenteric artery. A partial occlusion was produced by a hernia tape. This resulted in gangrene of the left lower extremity, which had to be amputated. Phantom limb pain resulted. Six months later the patient died of a rupture of an aneurysmal dilatation which formed proximally to the tape ligation.

Our experience with a cellophane cuff placed above an aortic aneurysm indicates that a gradual occlusion with spontaneous thrombosis of the sac may in favorable cases postpone the inevitable rupture of the aneurysm. Morton and Scott point out that traumatic aneurysms in young persons which are treated with partial occlusion by the Matas technic are the most favorable types to deal with. Obviously the ideal method has not yet been found.

In a timely and useful article, Beck discusses the syndrome of pulsating hematoma, a false aneurysm, since its wall is not lined with endothelium¹⁶⁵. It should be looked for in every puncture wound which is followed within twenty-four hours by a large swelling and pain of boring character. The swelling is hard and brawny, and the skin is glossy red above it. Nerves are

154 Learmonth, J. R., Blackwood, W., and Richards, R. L. Localized Arterial Thrombosis of Indeterminate Origin, *Edinburgh M. J.* **51** 1 (Jan) 1944.

155 Barker, N. W., and Hines, E. A., Jr. Arterial Occlusion in the Hands and Fingers Associated with Repeated Occupational Trauma, *Proc. Staff Meet., Mayo Clin.* **19** 345 (June 28) 1944.

156 Gage, I. M. The Technical Simplicity of the Matas Endo-Aneurysmorrhaphy, *Ann. Surg.* **119** 468 (March) 1944.

157 Wise, R. A. Traumatic Arteriovenous Aneurysm, *S. Clin. North America* **23** 1527 (Dec) 1943.

158 Penick, R. M. The Treatment of Traumatic Arteriovenous Aneurysms, *S. Clin. North America* **23** 1377 (Oct) 1943.

159 Pemberton, J. de J., and Black, B. M. Surgical Treatment of Acquired Aneurysm and Arteriovenous Fistula of Peripheral Vessels, *Surg., Gynec. & Obst.* **77** 462 (Nov) 1943.

160 Watson, J. R., and Miller, R. B. Arteriovenous Fistula of the Common Femoral Vessels with Extreme Dilatation of the External Iliac Vein, *Surgery* **14** 296 (Aug) 1943.

161 Langley, G. F. Gunshot Wound of the Innominate Artery, *Brit. M. J.* **2** 711 (Dec 4) 1943.

162 Handley, R. S., and Oldfield, M. Gunshot Aneurysm of the Carotid Artery, *Lancet* **2** 40 (July 10) 1943.

163 Harrison, P. W., and Chandy, J. A Subclavian Aneurysm Cured by Cellophane Fibrosis, *Ann. Surg.* **118** 478 (Sept) 1943.

164 Morton, J. J., and Scott, W. J. Ligation of the Abdominal Aorta, *Ann. Surg.* **119** 457 (March) 1944.

165 Beck, W. C. "Pulsating" Hematoma (False Aneurysm), *War Med.* **4** 502 (Nov) 1943.

often paralyzed by pressure, and there are signs of ischemia. The vessels most frequently involved, in order of their mention, are the femoral, axillary, popliteal, brachial, subclavian, and carotid arteries. Pulsation of the mass may be absent, but a systolic bruit is often heard on the proximal side of the hematoma. Treatment consists of early lateral suture of the artery with evacuation of the clot, or a late ligation of artery and vein. After three to six weeks enough collateral circulation may develop, but paravertebral sympathetic block should be routinely performed.

In the case of a 36 year old nonsclerotic, non-hypertensive male, the thoracic aorta ruptured as a result of severe trauma to the chest. The different causes of aortic rupture are discussed.¹⁶⁶ Holman¹⁶⁷ emphasizes the important principle that "a large artery should be ligated preferably just distal to a large collateral branch so that the full force of the arterial pulse-wave is not dissipated in purposeless distention of a blind segment and instead is directed into the main collateral vessel." He gives optional levels of ligation of the major arteries. Experimentally, he measured the pressure in the collateral vessels after ligating the femoral artery at various distances from the collateral supply and found incontrovertible experimental proof of the known clinical fact that an occlusion of the popliteal artery is more dangerous than one of the superficial femoral artery below the deep femoral artery. There are many valuable suggestions for the military surgeon regarding the management of vascular injuries based on the author's wide experience both in civilian life and recently at advanced Navy bases.

The Russian military surgeon Gnilyov¹⁶⁸ presents a personal series of 130 operations on blood vessels, comprising 98 operations for aneurysm and 32 for pulsating hematoma, he also operated in 23 cases of severe hemorrhage from a hematoma and in 9 for secondary hemorrhage in septic wounds. For two thirds of the patients ligation was employed, while the remainder had their injured arteries sutured. There was gangrene in 10 per cent of the former group and in none of the latter. The femoral artery was injured in 30 per cent, the tibial in 14 per cent, the popliteal and brachial artery in 9 per cent and the axillary in 7 per cent. The author advises against arterial suture between the fourth and the forty-fifth day after an injury. Local anesthesia is the

method of choice. The concomitant vein should be ligated. Arterial ligations for aneurysm are performed only when suture is impracticable. Post-operative physical therapy is important.

Another Russian surgeon, Pokotilov,¹⁶⁹ discusses secondary and erosive hemorrhage, a vexing problem with all war injuries, which is seldom seen in peacetime. While only 2 patients with such hemorrhage were seen during six years before the war, 25 were treated in two months when his clinic was functioning as an evacuation hospital. Certain arteries, such as the femoral, posterior tibial, gluteal and brachial arteries, were especially involved. In half of the cases bleeding was controlled by ligation of the bleeding point, in the other half the artery was tied proximal to the injury. Septic necrosis of tissue was the most frequent cause of secondary hemorrhage. He recommends immediate ligation of the bleeding point, with the vessel left in continuity. If a large artery has to be ligated, this should be done immediately below a large collateral vessel. If ischemia occurs after the ligation, sympathetic block with alcohol should be done.

Elkins and Woodhall¹⁷⁰ emphasize a most important principle in dealing with combined vascular and neural injuries. Instead of repairing these at different times, depending on what type of service the wounded man is apt to be in, they advocate an inclusive repair of all the injuries at one step. The repair of an aneurysm is never an emergency unless it is rapidly growing larger or has ruptured or cardiac failure is impending. Three to four months is a sufficient time for development of collateral circulation. Proximal compression of the vessels aids in the development of collateral circulation. Quadruple ligation with excision of the sac is the method of choice, and in suitable cases endoaneurysmorrhaphy may be practiced. This is an important contribution, and it is hoped that suitable teams will be available for such combined repairs.

COARCTATION OF THE AORTA

Blalock and Park¹⁷¹ divided the aorta in dogs, closed both ends and implanted the left subclavian artery into the aorta distal to its division. About 70 per cent of the animals lived more than six months and showed adequate flow of blood to the posterior portion of their bodies. The authors state that in man the enlarged collateral vessels which enter the aorta below its stenosis

166 Kleinsasser, L. J. Traumatic Rupture of the Thoracic Aorta, *Ann Surg* **118** 1071 (Dec) 1943

167 Holman, E. Further Observations on Surgery of Major Arteries, *Surg, Gynec & Obst* **78** 275 (March) 1944

168 Gnilyov, T. E. One Hundred and Thirty Operations on Blood Vessels, *Khirurgiya* **8** 40, 1942, abstracted, *Bull War Med* **4** 452 (April) 1944

169 Pokotilov, K. E. Secondary and Erosive Hemorrhage in Gunshot Lesions, *Khirurgiya* **8** 25, 1942, abstracted, *Bull War Med* **4** 452 (April) 1944

170 Elkins, C. D., and Woodhall, B. Combined Vascular and Nerve Injuries of Warfare, *Ann Surg* **119** 411 (March) 1944

171 Blalock, A., and Park, E. A. The Surgical Treatment of Experimental Coarctation (Atresia) of the Aorta, *Ann Surg* **119** 445 (March) 1944

would make the anastomosis more difficult but, on the other hand, because of the established collateral pathways the mortality in man should be low. In human patients the left common carotid artery could be used. Surgical treatment should be considered only for patients with a grave outlook, since coarctation of the aorta may be compatible with fairly long life. In fact, there are many well compensated minor coarctations which can be diagnosed only by detection of a difference between the blood pressures of the upper and lower extremities. This suggestion may find a place in the management of severe coarctations, perhaps facilitated by the vitallium tubes of Blakemore (see last year's review). We wish to emphasize, however, that the hypertension in the upper part of the body, which this procedure intends to counteract, may be partly on a vasoconstrictor basis, originating from the narrowed segment of the aorta, in such circumstances a bilateral dorsal sympathectomy, obviously not easy because of the collateral vessels, may prove useful. Such an operation has been suggested twice to young adults but not urged sufficiently to be accepted.

The Vasomotor System in Vascular Injury and Disease—A thought-provoking article on traumatic arterial spasm is published by Cohen.¹⁷² He states that smooth muscle responds to a stretch or to a minute injury with contraction which may persist so long that the arterial supply distal to the spasm becomes insufficient. The collateral circulation enlarges and acquires muscular and connective tissue, unless direct injury makes it spastic or a hematoma prevents its development. Since the muscle requires more blood than the skin, the spasm of the cutaneous vessels may be a protective reflex to divert blood to the deeper parts. Owing to the warming of the limb or to a sympathetic block, the likelihood of gangrene may be increased by upsetting this mechanism. When a nerve lesion accompanies a vascular lesion the incidence of Volkmann's ischemic contracture is higher because of sympathetic paralysis and diversion of blood to the skin.

He believes that the available anatomic and physiologic evidence is against the existence of a reflex arc whereby spasm from an injured artery spreads to affect the collateral vessels of the same limb. Failure of the collateral vessels to open may be due rather to injury and direct spasm of the collaterals, to hematoma or to spreading thrombosis. In the latter case arteriectomy proves most successful, for by it thrombi are removed or prevented from spreading.

Arterial spasm may develop not only because of a local, direct injury to smooth muscle but also as a result of a relatively minor local injury to the artery in association with other more severe injuries leading to the development of shock. This type of spasm is seen in the crush syndrome, as a result of tight tourniquets or when widespread reflex spasm can be produced from impulses arising in the skin or deeper tissue. On the basis of this conception and with the help of illustrative cases, the author concludes that there is little or no practical and no theoretic basis for sympathetic block in cases of traumatic arterial spasm.

We have cited this article in detail, since, published as the leading article in the *Lancet*, it deserves and has obtained widespread comment and interest. It would be most unfortunate, however, if this Hunterian lecture would deprive a number of patients with vascular injuries of the immediate application of a paravertebral sympathetic block. It is our belief that Cohen confuses the direct arterial stupor, which is rare and which one sometimes sees in manipulating an artery under spinal anesthesia, with the widespread vascular spasm following an arterial embolus or an arterial thrombus, whether traumatic or due to disease. It is true that the local response of an artery to stretch or mild trauma may be a prolonged spasm, which if it lasts long enough may progress to gangrene as in the case of Clark¹⁷³, it is also true that puncture of an artery may initiate a depressor type of reflex, as in the case of persons who have arterial punctures for removal of samples of blood. But it is hard to mistake these lesions for the chronic sensory-sympathetic reflexes which can be successfully interrupted by paravertebral block and which relieve pain and ischemia.

It is also true, however, that when the main blood supply of an extremity is shut off and arteriolar destruction in the terminal bed is widespread, as in certain forms of thromboangitis obliterans (Buerger's disease), a block of the sympathetic nerve supply may lower the cutaneous temperature of a toe and precipitate gangrene, since vasodilatation elsewhere uses up the available blood. Such a finding is a contraindication to sympathectomy without simultaneous amputation of the toe.¹⁷⁴ But in injuries to major arterial pathways the terminal bed is usually intact and should respond favorably to paravertebral sympathetic block. In fact, its use to decrease post-traumatic edema and improve

173 Clark, C. W. Traumatic Arterial Spasm, *Brit M J* 2 167 (Aug 7) 1943.

174 de Takáts, G. The Value of Sympathectomy in the Treatment of Buerger's Disease, *Surg, Gynec & Obst* 79 359 (Oct) 1944.

172 Cohen, S. M. Traumatic Arterial Spasm, *Lancet* 1 1 (Jan 1) 1944.

blood flow in the traumatized limb is still not as widely appreciated as it should be

The early treatment of frozen feet and hands by paravertebral block of the sympathetic nerve supply is advocated by Burk¹⁷⁵. He states that the primary response of the extremities to cold is vasoconstriction, followed by thrombosis. Unfortunately no figures are presented to demonstrate the results of this procedure. Our limited experience would indicate that this method has both therapeutic and prognostic value. If the temperature of the frozen digit does not rise, or especially if it falls after procaine block, the viability of the part is lost and amputation will have to be expected.

Telford¹⁷⁶ presents 5 cases of late stages of immersion foot and frostbite which exhibited vasospasm, excessive sweating or ulceration. The patients were greatly benefited by preganglionic sympathectomy. The pain ceased, and the ulcers healed. He advises preoperative sympathetic block, if a rise of 1 degree centigrade is observed. Sympathectomy is justified. On the upper extremity he employs ulnar nerve block at the elbow which, of course, affects only the fifth and partly the fourth finger.

Richards¹⁷⁷ writes an excellent article on the vasomotor disturbances in the hand after injury to peripheral nerves. He notes that the immediate effect of interruption of a nerve is vasodilatation which corresponds roughly to the zone of analgesia. The skin becomes hot, flushed and dry and does not respond to changes in environmental temperature. There is little or no response when other portions of the body are heated.

The cause of the subsequent fall in the temperature of the denervated part has not been fully explained. It is not due to sensitivity to epinephrine, since physiologic concentrations of this hormone produce a fall in temperature of not more than 3 or 4 degrees centigrade, whereas there may be a fall of 15 degrees centigrade after interruption of a peripheral nerve. The author suggests that the section of the nerve destroys the axon reflex which effects local dilatation as a response to trauma. This reflex can be obtained immediately after the section of the nerve but disappears as the sensory fibers degenerate. Lowered local metabolism may also account for the fall in temperature. It is significant that a superficial infection in a denervated digit may

produce so great a rise in local temperature that the affected digit becomes the warmest in the hand.

While complete section of a peripheral nerve is undoubtedly associated with sympathetic paralysis and its vasomotor and sudomotor phenomena, another type of vasodilatation is recognizable in partial nerve injuries, which responds to sympathetic block. This vasodilatation seems to be an irritative lesion of efferent vasodilators which produce a throbbing, vascular type of pain. This pain is aggravated by venous stasis and eliminated by arterial compression. It combines increased arterial pulsations with an increased peripheral resistance, much like a parasympathetic stimulant, such as neostigmine, produces. This is the vascular lesion encountered in the causalgic states, a frequently misunderstood syndrome¹⁷⁸.

The control of pain in post-traumatic and other vascular disturbances by sympathectomy is advocated by Mahorner¹⁷⁹. He believes that sympathectomy or repeated paravertebral block is indicated for post-traumatic pain caused by vasospasm and edema in causalgia, for Sudeck's atrophy, for sympathalgia, and for nontraumatic reflex vasospasm from inflammatory thromboses or emboli. He does not believe that Raynaud's disease is helped by sympathectomy, but he advocates the operation in cases of thromboangitis obliterans (Buerger's disease) for patients below the age of 50.

Learmonth and his co-workers discuss vasomotor disorders of the limbs in wartime¹⁸⁰. Arterial spasm resulting from arterial injury is difficult to differentiate from arterial thrombosis, it is unaffected by proximal periaarterial sympathectomy and ganglionectomy. Obviously damaged segments should be excised and local heat should be avoided, uncomplicated arterial spasm recovers spontaneously.

Traumatic arteritis occurs mostly in young persons, with resulting thromboses producing progressive ischemia. This is best treated by preganglionic sympathectomy followed by excision of the thrombosed segment of the vessel, if this is feasible. Traumatic venous thrombosis may give rise to reflex arterial constriction which

178 de Takáts, G. Nature of Painful Vasodilatation in Causalgic States, *Arch Neurol & Psychiat* **50** 318 (Sept) 1943.

179 Mahorner, H. The Control of Pain in Post-traumatic and Other Vascular Disturbances (the Role of the Sympathetic Nervous System in the Treatment of, *Peripheral Vascular Diseases*), *Ann Surg* **119** 432 (March) 1944.

180 Learmonth, J. R., Ungley, C. C., Blackwood, W., Gaylor, J. B., Green, R., and Lewis, T. Discussion on Immersion Injuries and Vasomotor Disorders of the Limbs in Wartime, *Proc Roy Soc Med* **36** 515 (Aug) 1943.

175 Burk, F. Novacaine Infiltration of the Sympathetic as Early Treatment for Frozen Feet, *Chirurg* **15** 347 (June) 1943.

176 Telford, E. D. Sympathectomy in Treatment of the Cryopathies, *Brit M J* **2** 360 (Sept 18) 1943.

177 Richards, R. L. Vasomotor Disturbances in the Hand After Injuries of Peripheral Nerves, *Edinburgh M J* **50** 449 (Aug) 1943.

can be relaxed by sympathetic block or sympathectomy

For organic vascular disease these authors recommend conservative therapy, but in selected cases sympathectomy may permit minor instead of major amputations. For the vasomotor disorders resulting from exposure to cold, only in the late stages is sympathectomy recommended. For the early stages of immersion limb, gradual warming and a conservative attitude toward amputation are advocated. The study of immersion limbs reveals wallerian degeneration of nerves, damage to muscles and fibrosis. But in the late stages failure of reflex vasodilatation occurs, and it is then that sympathectomy is of help.

An excellent description of the vasomotor phenomena accompanying injuries, especially thromboses, is given by Homans.¹⁸¹ Pain, ischemia, cyanosis, edema and atrophy of the tissues may be the result of reflex vasomotor phenomena originating from the site of the lesion. Cervical rib, a fracture or an injury of soft tissue may have similar effects. An injection into the appropriate sympathetic ganglia will temporarily abolish all signs and symptoms of the disturbance in circulation.

Trimble and his associates¹⁸² present a rather revolutionary idea of performing sympathectomies on patients from 50 to 60 years of age and even older who suffer from organic vascular disease, such as arteriosclerosis, thromboangitis obliterans, late results of exposure to cold, chemical burns, trophic ulcers or ununited fracture. They feel that even if vasomotor spasm as tested by sympathetic block is small, the conclusion that sympathectomy is useless is untenable. They present a convincing group of case histories.

Such attempts have been made by Atlas (see last year's review). That normal vasomotor tone and its fluctuations may have a deleterious effect on advanced vascular disease must be readily admitted. But if one fails to follow the lead of preoperative sympathetic block an acceleration of gangrene may follow. Our experience with a small group of arteriosclerotic patients over 60 years of age has been excellent. There is no doubt, however, that sympathectomy at this stage is bound to have a mortality and that if terminal arteriolar destruction is present, as in some frostbites or in patients with arteriolar disease, the condition may be aggravated by a diversion of blood from the obliterated arteriolar bed to areas which are better capable of vasodi-

lation. It is our feeling that carefully selected patients will respond well to this treatment, especially patients with presenile atheromatosis should be suitable subjects, since then lesions are not infrequently limited to the lower extremities and the arteriolar bed is comparatively free.

Mention should be made of the excellent review of White on the progress of surgery of the autonomic nervous system.¹⁸³ A review of this review is of course hardly feasible, but it should be read in the original. The indications and contraindications of sympathectomy for peripheral vascular diseases and for essential hypertension are discussed in detail.

SURGICAL TREATMENT OF HYPERTENSION

Schwartz and Findley¹⁸⁴ believe that surgical interruption of appropriate pathways is preferable to injection of alcohol into the segments. However, in cases in which there is doubt concerning the benefit to be derived from surgical procedures, a procaine block of the sympathetic ganglions from the ninth dorsal to the second lumbar segment on both sides is of prognostic value. The success of the injection is demonstrable by tests for sweating. It would be most welcome to have a clearcut preoperative test to determine the operability of hypertensive patients. Unfortunately such a widespread block of sympathetic ganglions is uncomfortable, requires sedation and may so depress venous return that elderly arteriosclerotic patients will show a good response to it although they are not among the patients suitable for operation. After a few trials we have abandoned the use of this method, which seems logical. Possibly a bilateral injection into the splanchnic nerves may be substituted, but this method has its dangers.¹⁸⁵

AMPUTATIONS

Amputations of lower extremities under refrigeration anesthesia have been reported by Massie,¹⁸⁶ Haley¹⁸⁷ and Bowers,¹⁸⁸ who all emphasize the advantages of depressing cellular metabolism, decreasing absorption from infec-

183 White, J. C. Progress in Surgery of the Autonomic Nervous System, *Surgery* **15** 491 (March) 1944.

184 Schwartz, H. G., and Findley, T. Preliminary Observations Concerning Paravertebral Injections of the Sympathetic System in Hypertension, *Surgery* **14** 267 (Aug.) 1943.

185 de Takats, G. Splanchnic Anesthesia, *Surg., Gynec. & Obst.* **44** 501 (April) 1927.

186 Massie, F. M. Amputation with Refrigeration Anesthesia, *South M. J.* **37** 1 (Jan.) 1944.

187 Haley, E. R. Arteriosclerotic Gangrene. A Report on Refrigeration Prior to Amputation, *Arch. Surg.* **46** 518 (April) 1943.

188 Bowers, W. F. Refrigeration Therapy in Vascular Trauma, *Mil. Surgeon* **93** 289 (Sept.) 1943.

181 Homans, J. Vasomotor and Other Reactions to Injury and Venous Thromboses, *Am. J. M. Sc.* **205** 313 (March) 1943.

182 Trimble, I. R., Cheney, W. S., and Moses, W. R. The Operative Attack on Organic Vascular Disease, *Surgery* **15** 655 (April) 1944.

tious or toxic material and minimizing the shock of the operation. Attention should be called, however, to the contribution of Richards,¹⁸⁹ who raises the obvious objection to the method, namely, the possibility of delayed healing of the stump. In our experience, refrigeration has effectively relieved pain and absorption of toxins from a limb which is to be amputated. Also, if delay is permitted, the patient's general status can be improved and his diabetic status can be treated, and even the collateral circulation is augmented by the fact that amputation is not necessary in the case of an acute vascular occlusion. Our experience, however, with having to amputate through refrigerated tissue has not been encouraging. There is unquestionable delay in union and exudation of plasma, a collar of cutaneous gangrene has been observed in a patient whose circulation was adequate at the level of amputation.

Kirk and McKeever¹⁹⁰ emphasize that closed amputations are dangerous to life and wasteful of stump length in the presence of established infection or potential infection. The local and systemic use of sulfonamide drugs and as yet of penicillin has not obviated these dangers. The present Surgeon General of the Army, Major General Kirk, has advocated the guillotine amputation followed by the use of continuous skin traction for amputations in the field. Simple plastic closure or reamputation at the site of election finally produces an excellent stump.

Jack and Chainley¹⁹¹ have used a delayed closure of the stump in the African theater of war. Flaps are prepared and sutures inserted over a pack of gauze saturated with sulfanilamide. After a few days the stump is reopened and a careful resuture of the skin is done, resulting in primary union. We have followed this method in a few cases of infected diabetic or arteriosclerotic gangrene and have been impressed by the rapidity with which primary union is accomplished after preliminary full drainage.

Pearl and Misrack¹⁹² report their experience with 36 amputations done for peripheral vascular disease. They use Pearl's modification of the Callender amputation. They emphasize the dangers of operating in the presence of inadequately controlled diabetes, of overoptimistic con-

servative management and of cellulitis superimposed on peripheral vascular disease.

In selecting cases for amputation, they cite the value of examining the peripheral pulses and the postural changes of color, but they deprecate the value of roentgen rays for demonstrating calcification of the peripheral vessels. They state that even the patient with completely controlled diabetes does not possess the resistance to surgical trauma found in the nondiabetic person. The average number of postoperative days for nondiabetic patients was thirty-seven and nine-tenths, compared with forty-six and three-tenths for the diabetic patients.

They cite the advantages of lumbar sympathetic block, their mortality was 13 per cent. Death occurred from toxemia, septicemia, bronchopneumonia and thromboembolism.

Our experience with the Callender amputation has been equally satisfactory, the patients are allowed to get out of bed the second or third day and sent home within a week, which permits a more rapid turnover of the hospital beds. They may, however, need visiting nursing care for the stump. The liberal use of sulfonamide drugs, blood transfusions and massive protein and vitamin intake greatly aids the convalescence of such patients.

Thompson¹⁹³ presents a practical and comprehensive survey of the subject of amputations, pointing out the characteristics of a satisfactory stump and describing the operations best fitted to fulfil these requirements at different levels. Poor stumps usually result from wrong choice of level or procedure, excessive damage to soft tissue, excess of soft tissue in the stump, closure under tension, failure to utilize traction or splinting and neglect of postoperative conditioning of the stump, joints, muscles and skin.

Certainly many details must be observed in order to produce the ideal stump. Among other things we have been impressed with the importance of adequate drainage of plasma and lymph for a few days postoperatively. Not only will infection result from retention of this material, but its retention will lead to a fibrous stump, which is painful, unwieldy and conducive to many other sequelae. The method of Callender first pointed to the importance of profuse drainage combined with the possibility of primary union, and this principle can be carried through in every location. Both refrigeration anesthesia and the use of dicoumarin (3,3'-methylene-bis[4-hydroxycoumarin]) sin against this principle, unless a two stage closure is used.

189 Richards, V. Refrigeration Anesthesia in Surgery, *Ann Surg* **119**:178 (Feb) 1944.

190 Kirk, N. T., and McKeever, F. M. The Guillotine Amputation, *J A M A* **124**:1027 (April 8) 1944.

191 Jack, E. A., and Charnley, J. Two-Stage Amputation. Primary Planned Amputation in the Presence of Sepsis, *Brit M J* **2**:131 (July 31) 1943.

192 Pearl, F., and Misrack, M. Atraumatic Amputation Through the Lower Thigh. Experiences with Its Use in Peripheral Vascular Disease, *Surg, Gynec & Obst* **77**:354 (Oct) 1943.

193 Thompson, V. P. The Amputation Stump from the Prosthetic Point of View, *J A M A* **124**:1036 (April 8) 1944.

White¹⁹⁴ describes in a timely contribution the management of painful amputation stumps. After the obvious causes of painful stumps are eliminated, there frequently remains an incapacitating pain due to irritation of end bulb neuromas. Phantom limb pain may or may not be associated with such neuromas. The persistence of pain and postural sensations similar to those experienced by the patient before amputation is assumed to be due to chronic, long-standing irritation of centrally conducting axons which produce an impression on the sensory cortex and are projected back to the area of irritation, which is now missing. These sensations, in the absence of pain, are so weak as a rule that only such portions as are richly endowed with sensory end organs and fibers will be represented in the phantom. As healing progresses, sensory impulses diminish and the phantom gradually disappears. Should abnormal conditions prevail in the stump, then the afferent impulses from the cut nerve persist and the phantom may retain its original position or may get increasingly painful.

For elimination of the phantom limb pain, the following procedures are tested: simple resection of a painful neuroma, sympathetic block, sympathectomy, section of the spinothalamic tract, excision of the sensory cortex and finally frontal lobotomy. As White points out, it is important to recognize the sensory level at which interruption of pain tract fibers is still efficacious. This problem well emphasizes the progressive character of intractable pain, which can be eliminated

early with comparatively simple measures but which ascends to higher and higher levels and may finally require ablation of the sensory cortex, as performed in the spectacular case of de Gutiérrez-Mahoney¹⁹⁵.

In our work, the resection of neuromas and their implantation into bone marrow¹⁹⁶ have so far been satisfying. Curiously, a patient who continued to have phantom limb pain after spinal anesthesia was relieved by sympathetic block followed by sympathectomy, an observation which permits several explanations. It seems to us likely that interruption of sympathetic fibers does not act by severing painful impulses, it may operate by neutralizing the burning, causalgic type of pain brought on by antidromic impulses which produce pain and vasodilator substances in the periphery.

Whether spinal anesthesia would simulate the effect of chordotomy is doubtful, since spinal anesthesia would hardly diffuse into the spinothalamic tract and actually paralyze only motor and sensory roots. However, a chordotomy would have to precede any intracerebral section.

The plight of such patients is so terrible, and drug addiction, suicide and mental deterioration so likely, that such heroic measures are justifiable. Certainly a psychiatric approach is worth while, but it has not seemed to be successful in our limited experience.

195 de Gutiérrez-Mahoney, C. G. The Treatment of Painful Phantom Limb by Removal of Postcentral Cortex, *J. Neurosurg.* **1** 156 (March) 1944.

196 Boldrey, E. Amputation Neuroma in Nerves Implanted in Bone, *Ann. Surg.* **118** 1052 (Dec.) 1943.

194 White, J. C. Pain After Amputation and Its Treatment, *J. A. M. A.* **124** 1030 (April 8) 1944.

Book Reviews

Lead Poisoning By Abraham Cantarow M D, and Max Trumper, Ph D Cloth Price, \$3 Pp 239 Baltimore Williams & Wilkins Company, 1944

The authors present what might veritably be considered a complete treatise on lead poisoning. They discuss the normal reactions of the body to lead, the pathologic changes in structures and functions occasioned by the presence of lead in the body, the clinical manifestations of lead poisoning and its treatment.

One chapter of importance to physicians who observe workers exposed to lead is the discussion on normal and abnormal levels of lead in the blood, body fluids and excretions.

In the last few chapters the authors discuss the occurrence of chronic lead poisoning, with special attention to industrial poisoning. The book concludes with a discussion of the technical analytic methods, both chemical and polarographic, of determination of lead in samples taken from the workroom atmosphere and in samples of urine and blood. A complete bibliography of the literature on lead poisoning is contained within the volume and probably is one of the most important features of a work of this kind.

One would hesitate to recommend this work to medical students, and I do not believe the authors intended it for them. The presentation of the literature from extensive sources, often with little attempt to clarify the present status of a particular phase of lead poisoning, would tend to confuse persons who have not had considerable experience with the subject. Also, the abstracting of actual clinical cases of lead poisoning and the describing of the various phases of onset, clinical course and laboratory findings would, if included, have tended to convey clinical recognition to a disease with protean manifestations. For the industrial physician, the biochemist and the industrial hygienist, however, this work is of considerable value.

Several features of the work deserve comment. The discussion of the pathologic physiology in the production of lead palsy is exceedingly well done. The authors point out that in recent years considerable evidence has been accumulating to oppose the long-held belief that prolonged exposure to lead causes significant elevation of blood pressure.

One must consider this the most encyclopedic work on lead poisoning yet to appear in the American literature.

Internal Medicine Its Theory and Practice in Contributions by American Authors Edited by John H. Musser, B S, M D, F A C P, Professor of Medicine in the Tulane University School of Medicine, Senior Visiting Physician to the Charity Hospital, New Orleans. Fourth edition. Price, \$10.00 Pp 1,518, with 26 tables and 70 illustrations. Philadelphia Lea & Febiger, 1945.

The editor, by way of preface to the latest edition of his book, reviews his own work. He says that the book was compiled originally for two purposes—to give medical students a textbook written by a limited number of well qualified authors and to give practitioners a properly documented work of references. These two purposes have been well fulfilled.

He goes on to say that the fourth edition includes many changes. The development of sulfonamide compounds, penicillin and thiouracil have necessitated a good deal of new writing, and so has the war, with its sharp focus on certain protozoan and metazoan diseases and on subjects like high altitude sickness or military neuropsychiatric disabilities, which hitherto seemed of no general importance. Thus this edition in many ways is a new book.

Finally, he acknowledges the value of the complete and thoroughly thought-out contributions from the thirty-three authors and coauthors who made possible the consummation of the avowed purposes of the volume. With this appraisal the reviewer for the ARCHIVES agrees wholeheartedly. The first and third editions have already been reviewed here (51 171 [Jan] 1933, 64 889 [Oct] 1939) and now the fourth is welcomed. As has been said previously, this work is an up-to-date textbook which opens up the vast field of medical knowledge in a manner both sensible and interesting. It deserves continued success.

Medico-Legal Blood Group Determination By David Hailey, M D. Price, \$3.50 Pp 119, with 13 illustrations and 23 tables. New York Grune & Stratton, 1944.

This compact volume will serve as a useful introduction to the subject with which it deals. Its contents are well organized and clearly presented. There is an adequate discussion of the theoretic background of the A, B and O and the M and N blood groups and the laws of inheritance of these factors.

A slide technic of grouping and typing is described which seems a little cumbersome in comparison to the use of test tubes, which many writers have found preferable, particularly for M and N typing. A brief history of the legal status of the tests for blood groups is included, and a report by the Select Committee of the House of Lords on the Bastardy (blood tests) Bill, which was under discussion before the war. This report will provide useful information to those interested in introducing such legislation in this country.

The technic of examining blood stains and secretions in the practical application of such findings seems to be somewhat brief and oversimplified. The final chapters are devoted to analyses of interesting histories of cases in which the author had the opportunity to examine stained specimens of blood and secretions.

Manometric Techniques and Related Methods for the Study of Tissue Metabolism By W. W. Umbreit, R. H. Burris and J. F. Stauffer. Price, \$3.50 Pp 198, with 29 tables and 42 figures. Minneapolis Burgess Publishing Company, 1945.

This book is intended for the beginning graduate student. It contains detailed descriptions of apparatus and technics for methods which have been found to be satisfactory in the laboratories of the authors and of their associates at the University of Wisconsin. It is not intended to be comprehensive but includes only methods which require a minimum of equipment. The Warburg respirometer and the differential manometer

are described in detail, with typical examples of their use and of the calculations involved. In addition, there are descriptions of Thunberg technics and electrometric methods for the determination of dissolved oxygen and for the determination of oxidation-reduction potentials.

The chapters "Methods of Tissue Preparation," "Manometric Estimation of Metabolites and Enzyme Systems," "Methods for the Analysis of Phosphorylated Intermediates" and "Preparation of Physiologically Important Intermediates and Metabolites" should be particularly valuable for the beginner in this field.

There are some inexact and ambiguous statements and some carelessness in mathematical notations which mar the first few chapters.

The Amino Acid Composition of Proteins and Foods. Analytical Methods and Results. By Richard J. Block and Diana Bolling. Price, \$6.50. Pp. 396, with tables and 1 figure. Springfield, Ill.: Charles C. Thomas, Publisher, 1945.

The authors of this monograph have gone to utmost pains to put together a vast amount of detailed knowledge concerning the amino acids which is timely and of clinical interest. The fact that their bibliography includes seven hundred references gives an idea of their careful work.

This type of book is unlikely to have any general appeal. It is the kind of work, however, which all investigators interested in biochemistry will utilize, particularly those clinicians who are especially concerned with nutrition. Above all, it will appeal to persons who undertake analysis of the amino acids, since appropriate methods are described so clearly. The medical profession for a long time to come will be indebted to the writers for this enterprise and for the scholarly manner in which they have completed it.

Los grandes síntomas o síndromes. Síntesis de terapéutica clínica. By Ambrosio Nijensohn. Pp. 366. Buenos Aires: Librería y editorial "El Ateneo," 1944.

The author presents a group of syndromes and symptoms which are frequently encountered by most physicians, classified by systems, such as respiratory, digestive or cardiovascular. The presentation is excellent, methodical and to the point, a brief discussion of the etiology, fundamental pathology and main symptoms is followed by a detailed description of the therapeutics involved.

At the end of each section is found a tabulated résumé of what has been presented in the previous pages. The bibliography is excellent and well arranged and com-

prises references from the world's literature. The book is of value mostly to the general practitioner as a means for quick reference in the treatment of certain common conditions.

The Gastro-Intestinal Tract. A Handbook of Roentgen Diagnosis. By Fred Jenner Hodges, B.S., M.D. Price, \$5.50. Pp. 320, with illustrations. Chicago: The Year Book Publishers, Inc., 1944.

The author of this small volume indicates that it is his desire to present information to assist the physician in choosing and interpreting roentgenograms of the gastrointestinal tract.

His object is accomplished in 320 pages, half of which are devoted to reproductions of roentgenograms and the rest to a discussion of these, together with suitable references.

The reviewer feels that not only practicing physicians but many roentgenologists can profit from reading this handbook.

Microbiology and Pathology. By Charles F. Carter, M.D. Third edition. Pp. 777, with 200 illustrations and 20 colored plates. St. Louis: C. V. Mosby Company, 1944.

In general, it is more difficult to write about medicine for nurses than for physicians, as the former are less likely to have an adequate background in the fundamental sciences. This book seems to accomplish very well its purpose of explaining in a simple way the fundamental concepts of bacteriology and pathology for nurses. The illustrations are abundant and adequate, and there are a glossary and an index.

News and Comment

NEW YORK INSTITUTE OF CLINICAL ORAL PATHOLOGY

An open meeting of the New York Institute of Clinical Oral pathology will be held at the New York Academy of Medicine, 2 East One Hundred and Third Street, New York, at 8:15 p.m., Monday, April 30, 1945. There will be a symposium entitled "A Survey of the Antibiotic Problem," in which seven outstanding physicians will take part. Further information may be procured from the Executive Secretary, 101 East Seventy-Ninth Street, New York 21.

ARACHNODACTYLY (SPIDER FINGERS)

H GRAY, M D

SAN FRANCISCO

Nearly half a century ago there appeared the first report (Marfan, 1896)¹ on a developmental anomaly which was well described as a congenital deformation of the four extremities characterized by long and slender bones. The names applied to the condition have been spider fingers, arachnodactyly or arachnodactylia, dolichostenomelia, and hyperchondroplasia (by way of contrast with achondroplasia). Subsequently other congenital disabilities have been associated: dislocation of the lens, cardiac defects and feeble-mindedness. More than 200 cases are said to have been reported in the literature, and the condition is indeed not rare, since 4 patients have been called to my attention by members of the staff within the last two years. Judging by a survey of a dozen reports in print,² one is surprised by the scarcity of anthropologic measurements, since these would certainly permit the earlier and more accurate recognition of cases now clinically missed. In some of the reports

of cases the diagnoses were not warranted by the measurements given, in many of the cases the measurements were fragmentary, perhaps only of one finger or even of one phalanx, and, finally, in most cases the landmarks used were so obscure as to prevent comparisons by the reader. Some sounder evidence, partly computed from observations in the literature but mainly from my own observations, together with the more notable clinical complications, will now be presented systematically from the aspect of the build of the patient.

REPORT OF CASES

CASE 1 (Joe G.)—Family History—Arachnodactyly was not known to be present in the grandparents, the parents or the five siblings, who ranged in age from 12 down to 4 years. Similar statements are common about reported cases but should be regarded skeptically, more than once 4 instances in the same family have been reported (Weve, 1931)^{2a}, hence it is probable that a number of the instances in the literature stated to be isolated could have been demonstrated to be really familial if measurements had been made of the immediate relatives. However, I have not had the opportunity to record these measurements for the 4 new cases.

Personal History—This boy, the third among six children of a Dalmatian mother and a Portuguese father, was born Dec 1, 1933 and was 10 years old when he was studied in Stanford University Hospital. There was no peculiarity about pregnancy or birth. His birth weight was 9 pounds (4,082 Gm). Also his hands, feet and ears were noticed at once as large, and the nurses called him "infant Hercules."

At 1 year his difficulty in seeing was noticed, and this deficiency has progressed and is now the chief complaint. Early in his infancy the frailness of the musculature was observed. At 5 he had to have special shoes, partly because of the length but mainly because of the extraordinary narrowness of his feet. At 6 he entered school, where he has been cooperative and is now, with some outside help from the teachers, in the fourth grade. At 7 he had some kind of disorder of the kidneys which vanished within a year.

Examinations—The physical and neurologic examinations were made by Dr Frederick A. Fender, who referred the patient to me for a study of his build. Little was found amiss. The patient appeared of normal intelligence. There was underdevelopment of the biceps, triceps and of the muscles of the forearms, thighs and calves. There was slight ataxia on the finger to nose test bilaterally. The biceps and triceps reflexes were absent.

Aided by the Rockefeller Fluid Research Fund

From the Department of Medicine, Stanford University School of Medicine

1 Marfan, A. B. Un cas de deformation congenitale des quatre membres, plus prononcée aux extrémités, caractérisée par l'allongement des os avec un certain degré d'amincissement, Bull et mem Soc méd d hôp de Paris **13** 220 (Feb 28) 1896.

2 (a) Mery, H., and Babonneix, L. Un cas de deformation congenitale des quatre membres. Hyperchondroplasia, Bull et mem Soc méd d hôp de Paris **19** 671 (July 4) 1902. (b) Achard, C. Arachnodactylie, Bull et mem Soc med d hôp de Paris **19** 834 (Oct 10) 1902. (c) Borger, F. Ueber zwei Falle von Arachnodaktylie, Ztschr f Kinderh **12** 161, 1915. (d) Young, M. L. Arachnodactyly, Arch Dis Childhood **4** 190 (Aug) 1929. (e) Weve, H. Ueber Arachnodaktylie, Arch f Augenh **104** 1 (May) 1931. (f) Huber, J., Lièvre, J. A., and Hector. Arachnodactylie, Bull Soc pédiat de Paris **35** 49 (Jan 19) 1937. (g) Roederer, C. Un cas d'arachnodactylie, ibid **35** 225 (April 20) 1937. (h) Roch, M. Arachnodactylie, Presse méd **45** 1429 (Oct 9) 1937. (i) Olcott, C. T. Arachnodactyly (Marfan's Syndrome) with Severe Anemia, Am J Dis Child **60** 660 (Sept) 1940. (j) François, J. De la pathogenie et de l'origine hypophysaire du syndrome de Marfan, Bull et mem Soc franç d'opht **48** 157 (May 13) 1935. (k) Roederer, C. Un cas larvé de dolichostenomélie, Bull Soc pédiat de Paris **36** 269 (April 26) 1938. (l) Marfan¹.

The psychologic examination was made by Dr Hale Shirley, who reported that the intelligence quotient was 90 and was reasonably accounted for by the difficulty in vision.

The urine was normal.

The examination of the eyes by Dr Jerome W Bettman revealed that the chief complaint was nearsightedness which had been present from infancy. External inspection revealed noticeable smallness of the pupils, probably congenital. Such miosis is a part of the syndrome found in association with dislocated lenses and arachnodactyly. Severe iridodonesis (tremulous movements of the iris), pathognomonic of subluxation, dislocation or absence of the lens, was noted in each eye. As the pupils did not dilate well with homatropine hydrobromide cycloplegia, careful examination of lenses and fundi was carried out with difficulty. The lenses were subluxated and still in the patellar fossa. The optic disks and surrounding areas appeared to be within normal limits. With uncorrected vision Joe was able to count fingers at 6 feet (18 meters) with the right eye and at 8 feet (25 meters) with the left eye. Retinoscopy with homatropine cycloplegia disclosed between 20 and 25 diopters of myopia in each eye. Correction of the refractive error improved the vision only to the extent

of the pediatric department. The observations on these 3, being partial, are merely shown in some of the tables and discussed incidentally. Most of what follows will refer to the patient in case 1, Joe G.

ARACHNODACTYLY AND OTHER ASPECTS OF BUILD

Inspection—Besides the points already noted, the patient, Joe, showed a funnel depression at the lower end of the sternum, as has been reported in earlier cases. The distribution of hair and of fat and the penis and testes were all normal.

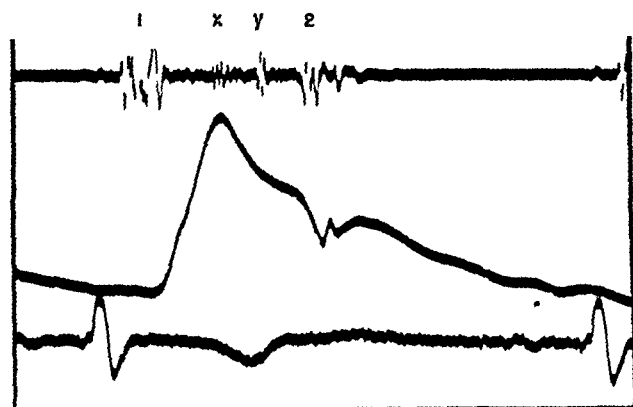


Fig 1 (case 1)—Extra cardiac sounds during systole

of allowing him to count fingers at 10 feet (3 meters), but a —20 D sphere was prescribed for each eye with the assumption that a portion of the visual difficulties might be due to congenital amblyopia, evidenced by the patient's inability to see clearly beyond the end of his nose without glasses. His parents were advised to bring him in again in approximately six months.

The cardiac examination was made by Dr J K Lewis, who reported "Examination of the heart showed a systolic murmur over most of the precordium and within the apex a pair of extra sounds during systole. Roentgenograms of the heart showed it to be normal in shape and at the upper limit of normal size. A diagnosis of the type of lesion could not be made." These extra cardiac sounds are put on record in figure 1.

This topic is being further studied by Dr D A Rytand. With regard to cardiac function, it may be added that the boy plays actively and has never had cyanosis or edema.

CASES 2, 3 and 4—Clinically these 3 patients showed no ocular or cardiac defects but were called to my attention by Dr Lloyd B Dickey. The patient in case 2, Kathleen S, aged 13, was measured by him. The measurements of the patients in case 3, Louis M, aged 13, and case 4, Loraine B, aged 6, were made by me from roentgenograms or taken from the records

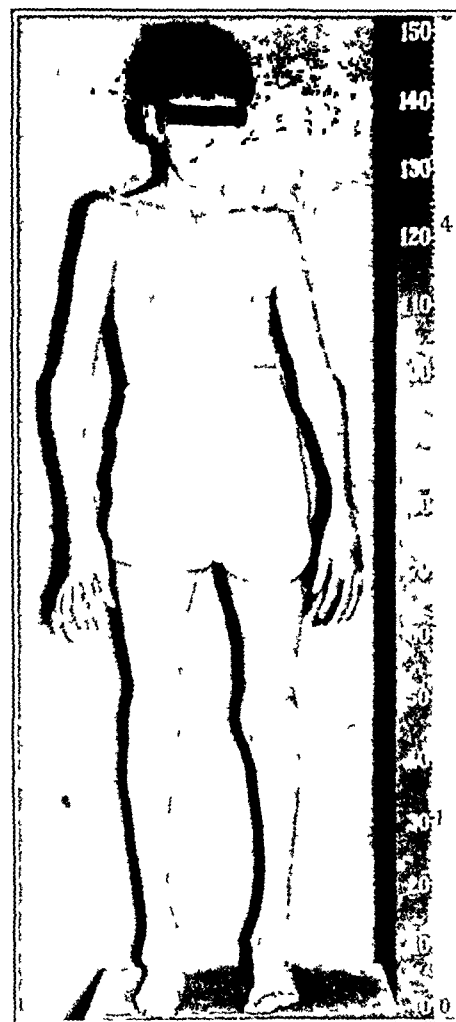


Fig 2 (case 1)—General appearance of the patient

enough. His general appearance is shown in figure 2.

Methods of Measurement—All measurements were made on the naked patient. The landmarks and technic follow anthropologic authorities, but, as even they differ in certain items, the specifications are recorded. The body and head were measured by the method of Hrdlička,³ except for the head height, which was done with Todd's head spanner. All details may be found in earlier

3 Hrdlička, A. *Anthropometry*, ed 1, Philadelphia, Wistar Institute of Anatomy and Biology, 1920, pp 79-81, ed 2, 1939, p 97.

publications (Gray and Ayres, 1931)⁴ special circumferences (Bayer and Gray, 1934),⁵ hand (Bayer and Gray, 1933),⁶ arm, foot, leg and segments (Kaslow and Gray, 1941,⁷ Gray, 1941)⁸ and foot breadth (Hrdlička, 1920, 1939³ and Gray, 1937)⁹

Normal Standard—The choice of a standard of reference with which to compare a patient of peculiar build is apt to be controversial. In this instance one would wish a standard based on boys aged 10 years, the offspring of Portuguese fathers and Dalmatian mothers, brought up under the conditions of life on a fruit ranch in Santa Clara County. No such standard is available. I shall use a standard based on measurements of 173 boys aged between 9.5 and 10.5 years, of mixed racial stocks, mostly third generation native born. Their economic status was higher than the patient's, but his was not at all impoverished, inasmuch as he was brought to the hospital as a private, not a ward, patient. Furthermore, the standard was based on our own observations (Gray and Ayres, 1931)⁴ and therefore corresponds precisely as to technic. Since private school children are notably tall and slender for their age, their standard is more appropriate than might be thought at first, because it is less likely than most standards to exaggerate the unusual tallness and slimness of the patient. This standard will be referred to hereafter as the norm. For the other cases to be discussed, various standards were used but will be omitted here.

Methods of Interpreting the Measurements—The measurements will be displayed in several tables. For the sake of the reader, however, only the more significant items will be selected for discussion. Occasionally the absolute values will be emphasized, but for the most part the patient's dimensions will be related to the norm. In order to avoid tedious repetition, the following

4 Gray, H., and Ayres, J. G. *Growth in Private School Children, with Averages and Variabilities Based on 3,110 Measurements on Boys and 1,473 on Girls*, Chicago, University of Chicago Press, 1931, chap. 3, p. 90.

5 Bayer, L. M., and Gray, H. *Anthropometric Standards for Working Women*, Human Biol. 6:472 (Sept.) 1934.

6 Bayer, L. M., and Gray, H. *The Hand Method of Measurement*, Am. J. Phys. Anthropol. 17:379 (Jan.-March) 1933.

7 Kaslow, A. L., and Gray, H. *Segment-Proportions in the Extremities, with Special Reference to Tall Men and Giants*, Growth 5:385 (Dec.) 1941.

8 Gray, H. *Leg-Length. A Survey of Methods Together with New Conversion Equivalents*, Growth 5:373 (Dec.) 1941.

9 Gray, H. *The Minneapolis Giant*, Ann. Int. Med. 10:1669 (May) 1937.

expressions will be used repeatedly, and are therefore now specified.

1 Absolute measurement, mainly in millimeters (table 1).

2 Relative measurement, as a percentage of stature.

3 Segment proportion, the proportion which a member such as the hand bears to the whole extremity such as the total upper extremity from the acromion to the tip of the midfinger.

4 Rank or percentile, the position of the patient among 100 normal boys of his age. This rank will be a most useful expression to the reader throughout the text. The method of calculation is that usual in statistical work and will therefore be omitted, save for a single explanation for any one who may wish the detail.

TABLE 1—*Routine Data on the Build of Patient Joe G., Case 1*^{*}

Measurement		Absolute in Millimeters	Relative in Percentage of Stature
Stature	S	1,545	100.0
Sitting height	Si	763	49.4
Chest circumference	O	684	44.3
Transverse	T	246	15.9
Anterior posterior	AP	156	10.1
Module	Chm	201	13.0
Shoulder biacromial	BA	320	20.7
Pelvis biacromial	BC	277	17.9
Head length	L	183	11.8
Breadth	B	148	9.6
Height	OH	122	7.9
Module	OM	151	9.8
Face height	VN	108	7.0
Breadth	BZ	128	8.3
Module	FM	118	7.6
Nose height	NH	48	3.1
Breadth	NB	28	1.8

* Weight (W) in kilograms is 35.0, in relation to stature in centimeters, 22.7.

Body and Head—The set of dimensions for routine study of build and growth, as picked from the vast number available in the physical anthropologic authorities, was used in our first monograph, in 1931,⁴ and still proves satisfactory. For this patient, these are put on record in table 1.

COMMENT

His weight in absolute terms (kilograms) was practically normal for his age. If it is related to his tall stature, however, by computation of a weight-stature index ($W [Kg] / S [cm]$) it is found that his relative weight is low, nearly down to the twenty-ninth percentile, that is to say, 29 per cent of boys of his age would be still thinner. (Following is the method of computation.) His weight-stature index is 22.7. The normal index for boys of 10 years [given in the

table in our monograph] is 24.4, hence his index is 1.7 below normal [$22.7 - 24.4 = -1.7$]. This deviation divided by the standard deviation [3.1], the conventional unit for assessing deviation, equals -0.55 [$-1.7 - 3.1 = -0.55$]. When this value for x/σ is referred to a probability table, the patient's percentile rank is found to be 29.1).

His height is above the mean by 13 cm (5.1 inches), this deviation putting him nearly up to the 99 percentile, that is, only 1 per cent of boys of his age would be expected to be taller. Hence, he is extremely tall but not a giant.

The bicristal width of the pelvis, 277 mm, was most extraordinary and was therefore remeasured the next day with a different pair of calipers, by way of confirmation. The relative value of bicristal width to stature (BC/S) was 17.9 per cent. Both these values, absolute and relative, are larger than those shown by any of the 173 normal controls aged 9.5 to 10.5 years, and even larger than those of any one of the next older group of normal controls, 201 boys between 10.5 and 11.5 years. Even in our normal girls, the magnitude 277 mm was not reached as an average until the group of girls aged 17.5 to 18.5 years. Whether the patient's pelvis was feminine in other respects was not studied. His genitalia, as remarked already, were not particularly small.

The biacromial diameter or shoulder breadth was, on the contrary, narrow. The relative value of the biacromial width to the stature (BA/S) set his position at the 19 percentile, that is, 19 per cent of normal boys would probably be even more narrow-shouldered.

The rest of the dimensions of his body and head will be most easily grasped by the reader when presented in relative terms as percentages of stature or as the patient's position in rank among his fellows. Thus, the transverse diameter of the chest in relation to the stature (T/S) at 15.9 per cent of stature was normal, which put him practically on the 50 percentile. All the remaining relative dimensions were smaller than normal and placed the patient in progressively lower rank, relative weight at 29 percentile, shoulder breadth and nose height at 19, chest circumference at 16, then anteroposterior chest depth, head breadth and bizygomatic breadth of face at 7 and mentonasion face length at 6. The remainder placed him at lower than the 1 percentile, that is, fewer than 1 boy in 100 would have as low a measurement as the patient. These items were relative sitting height, relative head length, relative head height and relative nose breadth. There is, in short, distinct evi-

dence of microcephaly, apparently a new finding in connection with arachnodactyly.

The indexes in table 2 may now be considered. The amazing one is the trunk breadth index, bicristal to biacromial (BC/BA), 86.6 per cent. This disproportion between the upper and lower ends of the trunk is so rare as to occur, I believe, less often than once in a thousand persons, and probably even less than that. The other

TABLE 2—Routine Indexes for Patient Joe G, Case 1

Index	Percentage	
Chest	AP/T	63.4
Transverse breadth	BC/BA	86.6
Cephalic	B/L	80.9
Face	MM/BZ	84.4
Face/head length	MM/L	59.0
Face/head breadth	BZ/B	86.5
Nose	NB/NH	58.3

indexes worthy of comment are slenderness of the nose, the nasal index or breadth to height (NB/NH), 58.3 per cent, which put the patient at the 12 percentile rank, and the flat chest index, anteroposterior to transverse (AP/T), 63.4, a figure which placed the patient at the 4 percentile rank.

Girths of the Extremities—The measurements both absolute and relative, are shown in table 3,

TABLE 3—Girths of Extremities

		Norm* (1)	Joe (2)	Ratio (3) (2)/(1)
		Absolute Measurement		
Extremity		Mm	Mm	
Thigh	Tg	405	372	0.92
Calf	Cf	283	232	0.82
Upper arm	UA	202	188	0.93
Forearm	LA	205	184	0.89
				Average 0.89
		Measurement in Relation to Stature		
		Per Cent		
		Per Cent	Per Cent	
Thigh	Tg/S	26.7	24.1	0.90
Calf	Cf/S	18.7	15.0	0.80
Upper arm	UA/S	13.5	12.2	0.92
Forearm	LA/S	13.7	11.9	0.87
				Average 0.87

* The nearest norm for boys of average stature, 1,515 mm, may be found in Martin,¹⁰ page 292.

together with some standards taken as the nearest approach (Martin)¹⁰. It is plain that our patient has remarkably slender muscles. For these items no ranks can be stated, because no standard deviations are at hand.

10 Martin, R. *Lehrbuch der Anthropologie*, ed. 2, Jena, Gustav Fischer, 1928, vol. 1, pp. 390, 396-399, 419 and 421.

Hand and Fingers—The data are in table 4. The measurements on the patient were made partly on the living hand, partly on an outline tracing and partly on a roentgenogram of the left hand. They are therefore quite accurate and

do by way of comparison seem to be to take the various items related to stature and to compare these relative measurements with the relative measurements of such normal controls as are available. The remarkable features are the

TABLE 4—*Hand Measurements*

Joe G Age 10 1 Years						Kathleen S Age 13 1 Years				Louis M 13 6 Years	Lorraine B 6 Years
		Absolute in Mm	Rela- tive in Percent- age of Stature	Norm in Percent age of Stature	Ratio (4)/(5)	Absolute in Mm	Rela- tive in Percent- age of Stature	Norm in Percent- age of Stature	Ratio (8)/(9)	Mm Years	Mm Years
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Ray I = thumb	I	137	8 9	8 0	1 11	153	9 4	7 8	1 21	133	95
Ray II = index	II	179	11 6	10 6	1 09	198	12 2	10 5	1 16	166	129
Ray III = hand L	HL	186	12 0	11 1	1 08	206	12 7	11 0	1 15	171	130
Ray IV = ring	IV	181	11 7	10 5	1 12	195	12 0	10 4	1 15	163	122
Ray V = little	V	159	10 3	9 1	1 13	165	10 2	9 1	1 12	138	104
Finger length III	FL	95	6 2	5 5	1 12					87	60
Palm length	PL	91	5 9	5 5	1 07					84	70
Hand breadth	HB	72	4 7	5 0	0 93	78	4 8	5 0	0 96	80	64
Bistylod breadth	Bs	48	3 1	3 4	0 91						
Hand circumference (mc)	HC	171	11 1	11 9	0 93						
Palm circumference (max)	PC	175	11 3	12 5	0 91						
Wrist circumference (min)	Wr	130	8 4	9 6	0 88						
				Mm	(3)/(5)			Mm	(7)/(9)		
Stature in mm	S	1,545		1,415	1 09	1,626		1,617	1 01	1,529	1,181
			In Ratio to Stature in Cm		(4)/(5)		In Ratio to Stature in Cm		(8)/(9)		
		Kg				Kg				Kg	Kg
Weight	W	35 0	22 7	24 4	0 93	46 8	28 8	31 6	0 91	34 7	15 2

and lying among the values for giants as shown in the diagram in my paper on the Minneapolis giant (Gray, 1937)⁹ A convenient figure to hold in mind for the normal hand is about 11 per cent of stature The comparison may be expressed as the ratio of patient to norm, according to the values from table 4, as 120 divided by 111 = 1.08, or 8 per cent in excess of normal

The hand index at the foot of table 5, hand breadth to hand length (HB/HL), gives the ratio 72 to 186, or 38.7 per cent This may be compared with the index computed from the averages for hand length and breadth for our 16

may be carried in mind as agreeing with the run of values for sundry series in Martin's textbook But even if one should take his most extreme figure for Europeans, 160 per cent of stature, the patient is still longer footed From the viewpoint of slenderness, next, let us consider his foot index of breadth to length (B/L) of 28.8



Fig 3 (case 1) —Hands of the patient

TABLE 6—Hand Length in Percentage of Stature (Relative Hand Length, HL/S), Some Cases From the Literature

Observer	Patient	Sex	Age	HL/S	Ratio *
Roch 1937	Name not stated	F	29	13.8	1.26
Case 2 1944	Kathleen	F	13	12.7	1.15
Borger 1915	H. G.	M	9	12.0	1.16
Francois 1935	Name not stated	M	12	12.3	1.14
Mery 1902	Gabrielle	F	11	12.4	1.12
Case 1	Joe	M	10	12.0	1.08
Marian 1896	Gabrielle	F	5	11.7	1.07
Roederer 1938	Name not stated	F	13	10.9	1.03
Case 4	Lorraine	F	6	11.0	1.02
Case 3	Louis	M	18	11.2	1.01

* Ratio of relative measurement of patient to that of normal control

tall normal controls (Kaslow and Gray, 1941), which was 45 Taking the ratio patient to norm, one has 38.7 to 45.0, or 0.86, or 14 per cent narrower than expectation Or the patient's index may be compared with the lowest index given (Martin)¹⁰ for Europeans, namely Frenchmen at 42.7 Against this standard, the patient's slenderness is not so obvious but is still very definite

Foot—The relative foot length in table 5 is 16.8 per cent of stature, which may be compared with the relative foot length in our 16 tall controls at 15 per cent, or a ratio patient to norm of 1.12, or 12 per cent longer than expectation The relative foot length taken here as standard

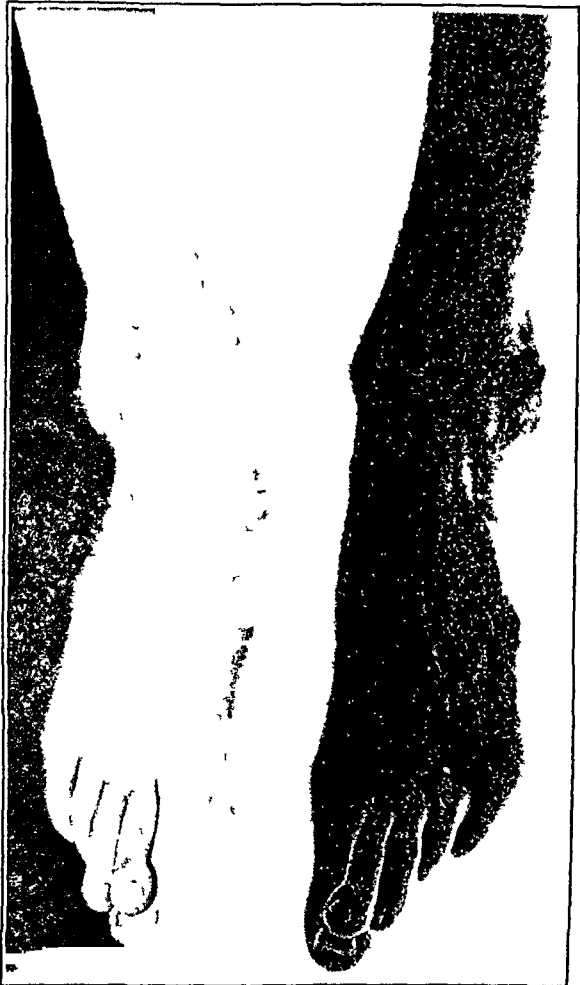


Fig 4 (case 1) —Feet of the patient

TABLE 7—Foot Length in Percentage of Stature, Some Cases from the Literature

Observer	Patient	Sex	Age	FL/S	Ratio *
Mery 1902	Gabrielle	F	11	17.6	1.16
Case 1	Joe	M	10	16.8	1.12
Roch 1937	Name not stated	F	29	16.3	1.10
Borger 1915	K. D.	F	1	16.4	1.09
Borger 1915	H. G.	M	9	15.8	1.05
Case 2	Kathleen	F	13	15.6	1.05
Marian	Gabrielle	F	11	16.2	1.04
Francois	Name not stated	M	12	15.5	1.03
Case 4	Lorraine	F	6	14.1	1.02
Case 3	Louis	M	18	15.3	1.01

* Ratio of relative measurement of patient to that of normal control

per cent against the lowest index given (Martin) for boys, namely 38.4, from which is obtained the ratio patient to norm of 0.75, or 25 per cent slenderness than expectation This is certainly an amazing foot

Segment Proportions in the Extremities—From these relations between limb length and

body length (stature), one must now distinguish the proportions between each of the three segments as against the total limb. This segmental viewpoint has been little documented in the literature, nevertheless, it is worth study (*a*) for pure science, (*b*) for possible use in estimating fitness for particular sports or particular occupations and (*c*) for diagnosis of abnormalities of growth, such as dwarfism or partial gigantism. A beginning in this direction was made in an earlier paper with reference to tall normal men and giants (Kaslow and Gray, 1941) ⁷

Pursuing this approach, with reference to the special form of partial gigantism called arachnodactyly, a ratio may be made between each segment proportion for the patient and the corresponding normal segment proportion as near as I have been able to estimate it. The computations discussed in the following paragraph in percentages of limbs are not tabulated in table 5, but, as a matter of record for comparison with the literature, which is more apt to state segments in percentages of stature, the more important data are so presented. One finds, then, that the patient's value for the hand (specifically, hand length from dactylion to carpale [da-ca] divided by total arm length of acromion to dactylion [ac-da]) to be in ratio to the normal value as 1.06:1, that is, 6 per cent longer, for the radius to be 1.01:1, that is, 1 per cent longer, and for the humerus to be 0.96:1, that is, 4 per cent shorter. In other words, the tentative implication is that arachnodactyly manifests a partial gigantism in the upper limb which is not of like degree in the three segments, but is progressively more pronounced as one proceeds away from the body.

For the lower extremity, however, surprisingly enough the reverse is found, since the inordinate

length is less noticeable distally. The details follow. The patient's value for the foot is to the normal value in the ratio of 0.86:1, that is, 14 per cent less, for the shank in the ratio 1.04:1, that is, 4 per cent longer, for the thigh in the ratio 1.20:1, that is, 20 per cent longer.

If another comparison is tried, by using as working unit the proportion of segment to stature, as in table 5, one finds confirmation both for arm and for leg segments. That is, in the arm the disproportion is more pronounced distally, whereas in the leg the disproportion is more pronounced centrally.

In connection with the hypothesis in the literature that this condition presents the opposite of achondroplasia, the segments should prove to be proportionately longer, the farther from the trunk they are. Evidence so far is equivocal. Discrepant findings for the two extremities are not solved by the few pertinent figures which I have found in the literature and have translated into ratios and shown in the last columns in table 5. For the paradox in the two extremities, then, I see no immediate explanation. It is to be remembered, however, that the technic of leg measurement, especially of the thigh segment, is more difficult than that for the measurements of the segments in the arm, and this difficulty may even cause unreliable observations.

SUMMARY

A 10 year old boy presented the rare anomaly arachnodactyly, or spider fingers, together with congenital dislocation of the lenses and a congenital cardiac peculiarity. A new contribution to the knowledge concerning this anomaly was made through a careful study of physical build by means of anthropologic measurements.

PRIMARY ATYPICAL PNEUMONIA OF UNKNOWN CAUSE

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Primary atypical pneumonia, or viral pneumonia, is not a new disease but has come into prominence because of its probable increased incidence, its lack of response to sulfonamide drugs and the more generalized use of roentgen therapy. The morbidity of this disease is at the present time four times that of the pneumococcal lobar type of pneumonia.¹ According to reports of the United States Army, the incidence of the disease is about 20 to 25 per cent of that of all infections of the respiratory tract² and above 50 and perhaps as high as 75 to 80 per cent of that of all pulmonary lesions.³ In the United States Navy the morbidity exceeds the figure for 1942, which was 2.79 per thousand.⁴ The loss of time in 738 cases in the air corps amounted to 20,000 man days, or 55 man years.⁵

EPIDEMIOLOGY

This disease, like many other infections, occurs in epidemics and is spread by direct contact only rarely. Perhaps the causative organism is disseminated by carriers or diseased persons who are "moist speakers" or impolite coughers. Diseased birds have been thought to be a source of infection.⁶ Coughing and sneezing animals, such as the cat, have been known to transmit the

disease to man.⁷ Laboratory workers after handling postmortem material have become ill with primary atypical pneumonia.⁸

As high as 50 per cent of the population of some communities have been involved, possibly because of a common viral agent.⁹ The degree of severity of infection varies with the depth to which the respiratory tract is involved, from acute rhinitis and tracheobronchitis to severe pneumonia.¹⁰ Not all persons exposed to the disease acquire it. Some having the same contacts acquire the disease in varying degrees of

Most of the work on this paper was done while the author was a civilian.

1 Rhoads, P. S. The Probable Incidence and Clinical Features of Virus Pneumonia, *Radiology* **40** 327 (April) 1943. Conlin, F. Atypical Pneumonia of Unknown Etiology. So-Called "Virus Pneumonia," *Nebraska M J* **28** 47 (Feb.) 1943.

2 (a) Dingle, J. H., Abernethy, T. J., Badger, G. F., Buddingh, G. G., Feller, A. E., Langmuir, A. D., Ruegsegger, J. M., and Wood, W. B. Primary Atypical Pneumonia, Etiology Unknown, *War Med* **3** 223 (March) 1943. (b) Lusk, F. B., and Lewis, E. K. Atypical Pneumonia of Unknown Etiology. A Clinical, Roentgenological and Pathological Correlation, *Dis of Chest* **10** 19 (Jan-Feb.) 1944.

3 (a) Green, D. M., and Eldridge, F. G. Primary Atypical Pneumonia, Etiology Unknown, *Mil Surgeon* **91** 503 (Nov.) 1942. (b) Allen, E. V., and Baird, L. W. Pneumonia in the Army, New Orleans *M & S J* **96** 177 (Nov.) 1943.

4 Smiley, D. F. The Incidence of Acute Respiratory Infections. The Experience of the U. S. Navy Since 1881, *U. S. Nav M Bull* **62** 17 (Jan.) 1944.

5 Owen, C. A. Primary Atypical Pneumonia. An Analysis of Seven Hundred and Thirty-Eight Cases Occurring During 1942, at Scott Field, Ill., *Arch Int Med* **73** 217 (March) 1944.

6 (a) Stickney, J. M., and Heilman, F. R. The Isolation of a Virus in Atypical Pneumonia, *Proc Staff Meet, Mayo Clin* **17** 369 (June 17) 1942. (b) Favour, C. B. Ornithosis (Psittacosis), *Am J M Sc* **205** 162 (Feb.) 1943. (c) Meyer, K. F., and Eddie, B. Spontaneous Ornithosis (Psittacosis) in Chickens the Cause of Human Infection, *Proc Soc Exper Biol & Med* **49** 522 (April) 1942. (d) Meyer, K. F., Eddie, B., and Yanamura, H. Y. Ornithosis (Psittacosis) in Pigeons and Its Relation to Human Pneumonitis, *Proc Soc Exper Biol & Med* **49** 609 (April) 1942. (e) Eaton, M. D., and Corey, M. Complement-Fixation in Human Pneumonitis with Group-Reactive Virus Antigens, *Proc Soc Exper Biol & Med* **51** 165 (Oct.) 1942. (f) Smadel, J. E. Atypical Pneumonia and Psittacosis, *J Clin Investigation* **22** 57 (Jan.) 1943. (g) Eddie, B., and Francis, T., Jr. Occurrence of Psittacosis-Like Infection in Domestic and Game Birds in Michigan, *Proc Soc Exper Biol & Med* **50** 291 (June) 1942. (h) Spink, W. W. Atypical Pneumonia, *Minnesota Med* **26** 337 (April) 1943. (i) Smadel, J. E., Wall, M. J., and Gregg, A. An Outbreak of Psittacosis in Pigeons, Involving the Production of Inclusion Bodies, and Transfer of the Disease to Man, *J Exper Med* **78** 189 (Sept.) 1943. (j) Meiklejohn, G., Beck, M. D., and Eaton, M. D. Atypical Pneumonia Caused by Psittacosis-Like Viruses, *J Clin Investigation* **23** 167 (March) 1944.

7 Baker, J. A. A Virus Obtained from a Pneumonia of Cats and Its Possible Relation to the Cause of Atypical Pneumonia in Man, *Science* **96** 475 (Nov. 20) 1942. Blake, F. G., Howard, M. E., and Tatlock, H. Feline Virus Pneumonia and Its Relation to Some Cases of Primary Atypical Pneumonia in Man, *Yale J Biol & Med* **15** 139 (Dec.) 1942.

8 Eaton, M. D., Beck, M. D., and Pearson, H. E. A Virus from Cases of Atypical Pneumonia. Relation to the Viruses of Meningopneumonia and Psittacosis, *J Exper Med* **73** 641 (May) 1941.

9 (a) Kornblum, K., and Reimann, H. A. The Roentgenological Aspects of An Epidemic of Acute Respiratory Tract Infection, *Am J Roentgenol* **44** 333 (Sept.) 1940. (b) "Acute Pneumonitis" Virus, editorial, *J A M A* **116** 1222 (March 22) 1941.

10 Lusk and Lewis.^{2b} Kornblum and Reimann.^{9a} "Acute Pneumonitis" Virus.^{9b}

severity¹¹ Longcope noted that persons with mild types of primary atypical pneumonia gave rise to the severer types in others, and vice versa¹² Thus it seems that there is individual variation in susceptibility to the disease In general, children and infants are more susceptible than adults, although the ages of higher incidence are those of young adults No age, however, is exempt Premature infants seem more susceptible than full term babies¹³ There is some seasonal variation The incidence is highest during cold, damp, changeable weather It is most common in the fall and early winter,¹⁴ and its morbidity is not affected by the increased incidence of the common cold¹⁵ or influenza¹⁶ The disease does occur in the tropics¹⁷

Outbreaks often occur in crowded areas, such as schools, armies, orphanages and jails Hos-

pitals may be included in this list, for several reports have stated that all groups of employees in hospitals have been involved¹⁸ This does not exclude the physicians or the nurses, who have a high rate of incidence, perhaps because of fatigue and repeated exposure

ETIOLOGY

Primary atypical pneumonia is a clinical entity with multiple causes This disease may be caused by (1) a number of viruses, (2) rickettsias,¹⁹ (3) a protozoan that produces toxoplasmosis,²⁰ (4) *Coccidioides immitis*²¹ and perhaps *Monilia*²² and (5) certain bacteria Among some of the early findings that suggested a virus as cause were bacteriologically sterile cultures of blood and of postmortem material and a decreased flora in the nose, throat and sputum—especially of virulent organisms The latter observation and also the low incidence of complications have led some workers to believe that patients with primary atypical pneumonia have an increased resistance to the pyogenic organisms²³ Laboratory work shows many of the viruses isolated from this and similar diseases to be antigenically related It has been thought that they may come from a parent strain²⁴ Mi-

11 (a) Dingle, J H, and Finland, M Primary Atypical Pneumonia of Unknown Etiology, *New England J Med* **227** 378 (Sept 3) 1942 (b) Reimann, H A An Acute Infection of the Respiratory Tract with Atypical Pneumonia A Disease Entity Probably Caused by a Filtrable Virus, *J A M A* **111** 2377 (Dec 24) 1938

12 Longcope, W T Pneumonitis or Virus Pneumonia, *Practitioner* **148**:1 (Jan) 1942

13 (a) Adams, J M Primary Virus Pneumonitis with Cytoplasmic Inclusion Bodies, *J A M A* **116** 925 (March 8) 1941 (b) Adams, J M Primary Virus Pneumonitis, Staff Meet, *Bull Univ Minnesota Hosp* **12** 414 (May 2) 1941 (c) Adams, J M, Green, R G, Evans, C A, and Beach, N Primary Virus Pneumonitis, *J Pediat* **20** 405 (April) 1942

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22 Dingle, J H, Abernethy, T J, Badger, G F, Buddingh, G J, Feller, A E, Langmuir, A D, Ruegsegger, J M, and Wood, W B, Jr Primary Atypical Pneumonia, Etiology Unknown, *Am J Hyg* **39** 67 (Jan) 1944

23 Goodrich, B E, and Bradford, H A The Recognition of Virus Type Pneumonia, *Am J M Sc* **204** 163 (Aug) 1942

24 (a) Rhoads¹ (b) Meyer and Eddie^{6c} (c) Eaton and Corey^{6e} (d) Smadel^{6f} (e) Horsfall, F L, Jr, Curnen, E C, Mirick, G S, Thomas, L, and Ziegler, J E, Jr A Virus Recovered from Patients

(Footnote continued on next page)

gration of some of the parasitic merozoites through the lungs has been known to produce atypical signs and symptoms of pneumonia²⁵. Again, interstitial pneumonitis has occurred in heat pyrexia²⁶. Some writers have noticed on culture an increase of viridans streptococci²⁷. Indeed, several cases of fatal pneumonia have been reported in which these organisms were responsible²⁸. Rhoads has shown experimentally that the more fulminating attacks of primary atypical pneumonia may be due to infection by a virus and viridans streptococci¹. Thomas and co-workers isolated a streptococcus (identified as no. 344) in 2 cases of primary atypical pneumonia which terminated fatally and showed that in 55 of 101 cases the patients had an increased titer to this organism²⁹. Some pneumococci are refractory to sulfonamide compounds³⁰. Gold stated that gonococci, staphylococci and pneumococci may become refractory to sulfonamide compounds if the patients are inadequately treated for as short a period as three days; moreover, the

organisms remain drug fast for a year or longer³¹. Again, even though adequate treatment with sulfonamide compounds is given, some pneumococci become refractory³².

PREDISPOSING FACTORS

Chilling commonly predisposes to the disease³³. Fatigue is also an important factor. Chronic diseases, such as chronic sinusitis and tonsillitis, have been thought to make the patient more susceptible. Malnutrition and lack of thiamine also seem to predispose to the disease³⁴.

PRODROMAL SYMPTOMS

A dry throat or a sensation of dryness while swallowing, malaise and weakness may be noticed five to ten days before the onset of other symptoms³⁵. A sensation of chilliness or a chill as well as fever may be noted a day or so before other symptoms appear. Thus a patient may have none or any one or more of these prodromal symptoms before the acute phase of the disease. There may be a cutaneous eruption early in the disease³⁶.

CHIEF COMPLAINTS

A cough or a "cold" is the most common complaint³⁷. Occasionally a patient calls the physician only because he has fever or because he is too weak to carry on his daily work. Other common complaints are headache, generalized muscular aches, pains in the chest, shortness of breath and abdominal pains.

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25 Keller, A. E. The Clinical Manifestations, Treatment and Prevention of Ascaris, *J Tennessee M A* **25** 346 (Sept.) 1932.

26 Smith, E. E. Heat Stroke a Thermoregulatory Incompetency with Pathological Findings, *U S Nav M Bull* **26**:479 (July) 1928.

27 (a) Longcope^{18d}. (b) Kneeland, Y., Jr., and Smetana, H. F. Current Bronchopneumonia of Unusual Character and Undetermined Etiology, *Bull Johns Hopkins Hosp* **67** 229 (Oct.) 1940.

28 (a) Solomon, S., and Kalkstein, M. Pneumonia Due to Streptococcus Viridans, *Am J M Sc* **205** 765 (June) 1943. (b) Thomas, H. M., Jr. The Role of Alpha Hemolytic Streptococcus in Pneumonia, *Bull Johns Hopkins Hosp* **72** 218 (April) 1943.

29 Thomas, L.; Mirick, G. S., Curnen, E. C., Ziegler, J. E., Jr., and Horsfall, F. L., Jr. Serological Reactions with an Indifferent Streptococcus in Pneumonia, *Science* **98**:566 (Dec 24) 1943.

30 Hamburger, M., Jr., Schmidt, L. H., Sesler, C. L., Rueggsegger, J. M., and Gruben, E. S. The Occurrence of Sulfonamide-Resistant Pneumococci in Clinical Practice, *J Infect Dis* **73** 12 (July-Aug.) 1943.

31 Gold, H. Some Recent Advances in Therapeutics, Including the Newer Drugs of the Sulfonamide Group, *Bull New York Acad Med* **19** 132 (Feb.) 1943.

32 Frisch, A. W., Price, A. E., and Myers, G. B. Type VIII Pneumococcus. Development of Sulfadiazine Resistance, Transmission by Cross Infection, and Persistence in Carriers, *Ann Int Med* **18** 271 (March) 1943.

33 Dingle and others^{2a}. Campbell, E. T. Primary Atypical Pneumonia and Malaria, *War Med* **3** 249 (March) 1943.

34 Pinkerton, H., and Swank, R. L. Recovery of Virus Morphologically Identical with Psittacosis from Thiamin Deficient Pigeons, *Proc. Soc Exper Biol & Med* **45**:704 (Nov.) 1940.

35 Rainey, W. G., and Burbidge, J. R. Acute Pneumonitis or Atypical Pneumonia, *Journal-Lancet* **59** 101 (March) 1939.

36 (a) Kneeland and Smetana^{27b}. (b) McKinlay, C. A., Lange, E. H., and Boehrer, J. J. Atypical Pneumonia Associated with Rheumatic Endocarditis, *Journal-Lancet* **62**:75 (March) 1942. (c) Prilla, E. Primary Atypical Pneumonia, Etiology Unknown, *Illinois M J* **83**:183 (March) 1943. (d) Hein, G. E., in Discussion of Primary Atypical Pneumonia, *Lancet* **1** 431 (April 3) 1943.

37 Lyght, C. E., and Cole, L. R. Pneumonia as It Affects Young Adults. Three Hundred Consecutive Cases Among Students at the University of Wisconsin, *Ann Int Med* **14** 2246 (June) 1941.

SYMPTOMS

The incubation period varies from five³⁸ to twenty-six²³ days. Reimann, however, expressed the opinion that in certain cases the incubation period is one or two days³⁹. The average duration is fourteen to twenty-one days, more precise observations show it to be seventeen to nineteen days^{2a}. The onset of the disease is usually insidious but may be acute in 25 to 33 per cent of the cases⁴⁰. Daniels, however, reported a sudden onset in all of his cases⁴¹.

In infants this disease may be secondary to measles and whooping cough⁴². The onset may be that of a cold or sneezing. The children are irritable or apathetic. On the other hand, the onset can be alarming and begin with cyanosis, dyspnea and high fever. Among 74 patients reported on by Adams and his co-workers,^{13c} 56 per cent of the infants with cough, dyspnea, cyanosis and high fever died, for those with a low fever the mortality rate was 20 per cent.

Cough is perhaps the most common symptom and occurs in about 85 per cent of all cases⁴³. It may appear at the onset of the acute phase or during the course of the disease. Often the cough starts with a rise of temperature. It may occur in paroxysms, especially at night. Changes in the temperature of the room and the patient's moving about in bed seem to stimulate the cough⁴⁴. It is often dry at the onset and may become productive later in the disease. The sputum is scant and may be mucoid, mucopurulent or even streaked with blood. The cough may

be so severe as to cause fatigue, excess sweating and muscular aches in the abdomen and chest. A burning sensation in the chest may be due to severe tracheitis or tracheobronchitis. Other pains in the chest that should be mentioned are those due to pleurisy and broken ribs, both of which occur rarely.

Headaches are commonly frontal or periorbital or affect the entire head. They are sometimes described as throbbing. Often these headaches are so severe that they do not respond to ordinary treatment. Not infrequently there is a burning sensation in the eyes. Lacrimation occurs only occasionally. Pain on rotation of the eyeballs, such as occurs in influenza, is rare and is though to be of aid in the differential diagnoses⁴⁵, yet soreness of the eyes on motion does occur not uncommonly⁴⁶. "Tiredness of the eyes" seems to be a part of the generalized weakness and the generalized muscular ache that are so commonly present. Accompanying the lack of strength there may be sweating, in the more severe forms the sweat is drenching. Frank chills are occasionally encountered, but most patients experience only a sensation of chilliness—often alternate chilliness and fever.

Dyspnea and cyanosis may occur on the fourth and fifth days of the disease²³. These symptoms may be evidence of bronchiolar and alveolar occlusion, atelectasis, a hyalin-like lining of the alveoli, edema and infiltration of the interalveolar tissue and possibly enlarged hilar lymph nodes. Other respiratory symptoms are rhinitis, pharyngitis and sometimes hoarseness and aphonia⁴⁷. The two last-mentioned symptoms may precede the onset of the disease and disappear a few days after the beginning of the illness. Other symptoms may be anorexia and occasionally vomiting, abdominal distention, constipation and diarrhea. Often return of appetite is the first sign of improvement.

The fever is usually of low grade, although the temperature may be as high as 105 or 106 F. Some patients may be entirely afebrile, this has been noted in infants^{13a} as well as in adults⁴⁸. The fever curve may be biphasic⁴⁹, i.e., there may be fever for one or several days (even up to

38 Kamin, H. N. Virus Pneumonia, Illinois M. J. 83 41 (Jan) 1943.

39 Reimann and Havens^{18c}. Reimann and Stokes^{18f}.

40 (a) Dingle and others^{2a}. (b) Duggan, L. B., and Powers, W. L. An Acute Respiratory Infection Resembling So-Called Acute Pneumonitis, J. Lab. & Clin. Med. 28 524 (Jan) 1943. (c) Goodman, S. Atypical Pneumonia, J. Oklahoma M. A. 35 504 (Dec) 1942. (d) van Ravenswaay, A. C., Erickson, G. C., Reh, E. P., Siekierski, J. M., Pottash, R. R., and Gumbiner, B. Clinical Aspects of Primary Atypical Pneumonia, J. A. M. A. 124 1 (Jan 1) 1944.

41 Daniels, W. B. Bronchopneumonia of Unknown Etiology in a Girls' School, Am. J. M. Sc. 203 263 (Feb) 1942.

42 (a) McCordock, H. A., and Smith, M. G. Intranuclear Inclusions: Incidence and Possible Significance in Whooping Cough and in a Variety of Other Conditions, Am. J. Dis. Child. 47 771 (April) 1934. (b) Goodpasture, E. W., Auerbach, S. H., Swanson, H. S., and Cotter, E. F. Virus Pneumonia of Infants Secondary to Epidemic Infections, Am. J. Dis. Child. 57 997 (May) 1939.

43 Lyght and Cole³⁷. Van Ravenswaay and others^{40d}. Kasich, M., and Cohen, I. S. Primary Atypical Pneumonia, J. M. Soc. New Jersey 40 358 (Sept) 1943.

44 Cass, J. W. Question of "Influenza" and Atypical Pneumonia, New England J. Med. 214 187 (Jan 30) 1936.

45 Bahlke, A. M. Some Differential Points in Diagnosis of Atypical Pneumonia of Probable Virus Origin, New York State J. Med. 43 315 (Feb 15) 1943.

46 MacLeod, C. M. Primary Atypical Pneumonia, M. Clin. North America 27 670 (May) 1943.

47 Reimann^{11b}. Reimann and Havens^{18c}.

48 Drew, Samuel and Ball^{19a}. Dingle and others²². Lyght and Cole³⁷.

49 (a) Lusk and Lewis^{2b}. (b) Adams^{13a}. (c) Schmitz, R. C. Primary Atypical Pneumonia, Wisconsin M. J. 43 228 (Feb) 1944.

seven days⁵⁰), and then the temperature may return to normal, with some remission of symptoms for a day or so, only to rise again with exacerbation of symptoms. The fever has a typical swinging character, i.e., the temperature is usually lower in the morning and higher in the afternoon or vice versa. Defervescence is usually by lysis but occasionally by crisis⁵¹. The fever, depending on the severity of the disease, may last from two^{15b} to forty-three⁵² days or even longer.

The heart rate is not increased in proportion to the rise in temperature as a rule. There may be bradycardia, or in more severe forms this slow rate may give way to a more rapid one during convalescence. Tachycardia may be present at the onset. Owen stated that a rise in pulse rate suggests an increasing pulmonary lesion and that a slow pulse, despite high fever, is little cause for concern⁵. The respiratory rate, as a rule, is only slightly increased. Herpes labialis and epistaxis are rare⁵³, however, Cutts reported that 23.4 per cent of his 60 patients had herpes labialis⁵⁴. Loss of weight and relapses are not uncommon. Berryhill and associates stated that 7 patients had recurrences within two years^{14c}. Dochez stated that 1 patient had as many as four relapses⁵⁵. Thus it would seem that as yet little can be said about immunity to this disease.

The amount of discomfort and the disposition of the patients vary. Malaise in the milder form of the disease may not be severe. Green reported the case of a soldier who while he had a temperature of 105 F was seen sitting up in bed, smoking and reading a comic strip^{3a}. It is obvious at once that such persons, who do not feel ill, are up and about doing their daily work for weeks and even months before they consult a physician. This is especially true if they are completely or nearly asymptomatic⁵⁶, in this event they seldom

seek medical aid. It is this group that is thought to be responsible for the spread of the disease^{15c}.

PHYSICAL CHARACTERISTICS

The nasal mucosa is often hyperemic, and the pharynx may be injected. The throat does not have the generalized edema seen in colds⁵⁷. In general, the physical manifestations in the chest are surprisingly few. In about 50 per cent of Green's 110 cases no abnormalities of the chest were found on the patients' admission to the hospital^{3a}. Dingle and co-workers could find no abnormal signs at any time in a few cases despite the fact that the location of the lesion was known²². Decreased breath sounds are more frequent than bronchial breathing. One may hear only fine or medium, moist rales in late inspiration. Often these rales do not appear until the temperature has fallen⁵⁸. In 57.2 per cent of 155 cases the first signs were presented within three days, in 27 per cent in four to seven days, in 5.5 per cent in seven to nine days and in 3.1 per cent in ten or more days^{15b}. Duggan reported that he had heard the initial rales in some of his cases as late as the eleventh day^{40b}. These may exist for several weeks after the patient has apparently recovered⁵⁹ and the roentgen plate cleared. At times rhonchi may be heard, especially during the later stages. In the more severe forms consolidation may be noted. Abdominal tenderness and rebound tenderness may be elicited. Occasionally the spleen and the liver are palpable.

PATHOLOGIC CHARACTERISTICS

Grossly the lung is crepitant, with isolated areas of pink or gray consolidation that vary in size⁶⁰. There may be hemorrhagic areas in the lungs⁶¹. Necrosis and ulceration of the epithelium may be found in the bronchi and bronchioles, with resulting cellular debris filling the lumens^{13a}. Often a thick exudate of mucus, desquamated cells, monocytes and a few neutrophils and eosinophils fills the small bronchi, bronchioles and alveoli. Beyond the obstruction there is atelectasis, in the other parts of the lung there may be emphysema. The blood vessels may be thrombosed^{28b} and necrotic and show periaarteritic changes^{27b}. An infarct in a lung has been reported^{14b}. Spread of the pulmonary lesion is not via the lumen of the respiratory tree but

50 Herxheimer, H. G. J., and McMillan, A. J. Atypical "Influenzal Pneumonia" at a School, *Brit M J* **2** 513 (Oct 31) 1942.

51 Dingle and others^{2a}. Lyght and Cole³⁷.

52 (a) Reimann^{11b}. (b) Shone, S., and Passmore, R. Pneumonitis Associated with Autohemagglutination, *Lancet* **2** 445 (Oct 9) 1943.

53 Needles, R. J., and Gilbert, P. D. Primary Atypical Pneumonia. Report of One Hundred and Twenty-Five Cases, with Autopsy Observations in One Fatal Case, *Arch Int Med* **73** 113 (Feb) 1944.

54 Cutts, F. B., and Lawson, H. A. Primary Atypical Pneumonia, Etiology Unknown, Rhode Island *M J* **27** 11 (Jan) 1944.

55 Dochez, A. R., in discussion on Reimann, Havens and Price^{24f}.

56 Owen⁵. Gallagher^{14c}. Andrus, P. M. Silent Bronchopneumonia, *Canad M A J* **47** 339 (Oct) 1942. Fredd, H. Atypical Pneumonias, *New York State J Med* **41** 34 (Jan 1) 1941. Ramsey, H., and Scadding, J. G. Benign Bronchopulmonary Inflammations Associated with Transient Radiographic Shadows, *Quart J Med* **8** 79 (April) 1939.

57 Primary Atypical Pneumonia, Etiology Unknown, *Army M Bull*, April 1942, no 61, p 31.

58 Dingle and others²². Miller, F. N., and Hayes, M. G. Bronchopneumonia of Mild Severity at University of Oregon, *Northwest Med* **38** 12 (Jan) 1939.

59 Longcope^{14b}. Shone and Passmore^{52b}.

60 Kneeland and Smetana^{27b}. Needles and Gilbert⁵³.

61 Adams^{13a}. Longcope^{14b}. Schmitz^{49c}.

rather by the interstitial tissue of the alveoli adjacent to the bronchioles.⁶² Bronchoscopy reveals a mucosa that is inflamed and congested and that bleeds readily, as compared with the moderately inflamed mucosa characteristic of pneumococcal pneumonia.²²

Microscopically one may see areas of hemorrhage in the lungs. The interalveolar tissue is edematous, thickened and infiltrated primarily by monocytes.^{27b} The alveoli in addition may have a hyalin-like lining.⁶³ Metaplasia of the alveoli has been seen.^{18d} Inclusion bodies have been found in the epithelial cells of the respiratory tract.⁶⁴ Adams reported that these bodies are found with increasing difficulty if the course of the disease has extended beyond several days or if a secondary infection has set in.^{13a} Gedgoud, however, reported the finding of inclusion bodies in a child who died of the disease after twenty-three days of illness. He also stated that he found these bodies in 25 of 35 women from whom he had taken vaginal and throat smears.^{64d} Inclusion bodies are not specific for viral infection, for they may be due to *Haemophilus pertussis*, *Pasteurella tularensis*, toxins, irritative chemicals^{24f} or the protozoan of toxoplasmosis.⁶⁵ Other pathologic changes noted have been hemorrhage of the adrenal glands,^{13a} acute splenic tumor,^{11a} focal necrosis of the liver,^{27b} acute follicular splenitis, necrosis of enlarged malpighian corpuscles of the spleen, edema of the meninges, mesenteric lymphadenitis²² and hyaline necrosis of the diaphragmatic muscle.⁵

LABORATORY FINDINGS

In general, during the early stages of primary atypical pneumonia there is a normal, slightly depressed white cell count or even a slightly increased count.⁶⁶ Cass, however, reported counts as low as 2,500 to 1,800.⁴⁴ He stated that those patients who have extremely low blood counts are severely ill, thus he concluded that the more severe the leukopenia in the early stages the worse the prognosis. Likewise any sharp rise of the number of white cells from leukopenia to

marked leukocytosis may be indicative of bad prognosis. McKinlay stated that so long as the original leukopenia is retained during the acute phase of the disease and is accompanied by consistently negative bacteriologic findings the prognosis is good.⁶⁷ An initial leukocyte count of 12,000 or higher was found to be due to "walking pneumonia," previous vomiting and secondary infection of the sinuses, ears, pharynx, etc.^{14a}

During convalescence it is common to have a leukocyte count of 10,000 to 15,000. The count may go as high as 20,000⁶⁸ or 22,000⁶⁹ and may be erroneously thought to be indicative of a secondary infection, but this is not the rule. Lyght and Cole pointed out that a rise in the white cell count, if it does not go too high, is usually a good sign.³⁷ The differential count reveals that the polymorphic neutrophils range between 65 and 90 per cent of the total count. According to Drye, lymphocytosis with 50 per cent lymphocytes is not uncommon. He also noted that the total white cell count began to rise the second or third day before the temperature fell and finally reached a peak two or three days after the temperature became normal.⁷⁰ In the series of infants at the University of Minnesota Hospital the average leukocyte count in 1937 was 19,140 with 48 per cent neutrophils, and in 1940 it was 13,500 with 47 polymorphic neutrophils.^{13b} Toxic granules may be seen in the cells, and there is usually a shift to the left. A differential count of 26 per cent eosinophils,⁷¹ 16 and 25 per cent monocytes⁷² and a few granulocytes has been encountered.⁷¹ Reimann found stippled erythrocytes and Dohle bodies in neutrophils.^{11b}

Other laboratory findings are increase of pressure of the cerebrospinal fluid to 250 mm of water,⁷³ increase in the number of spinal fluid

67 McKinlay, C. A., and Cowan, D. W. Acute Respiratory Infections Including Lobar Pneumonia and Atypical Pneumonia in a Young Adult Group, *Journal-Lancet* **61** 125 (April) 1941.

68 (a) Murray.^{14a} (b) Langille, J. A. Acute Pneumonitis or Virus Pneumonia, *Nova Scotia M. Bull.* **21** 333 (Nov.) 1942.

69 Smiley, Showacre, Lee and Ferris.^{11d} Solomon and Kalkstein.^{28a} McKinlay and Cowan.⁶⁷ Langille.^{68b}

70 Drye, J. C., in discussion on Flexner and Garson.^{125f}

71 Contratto, A. W. So-Called "Atypical Pneumonia" Among College Students, *New England J. Med.* **229** 229 (Aug. 5) 1943.

72 (a) Shone and Passmore.^{52b} (b) Collier, G. W. Virus Pneumonia, *Permanent Found M. Bull.* **1** 45 (Oct.) 1943. (c) Young, L. E., Storey, M., and Redmond, A. J. Clinical and Epidemiological Features of an Outbreak of Primary Atypical Pneumonia of Unknown Etiology Among Hospital and Medical School Personnel, *Am. J. M. Sc.* **206** 756 (Dec.) 1943.

62 (a) Green and Eldridge.^{3a} (b) Saphir, O. Pathological Changes in So-Called Atypical Pneumonia, *Radiology* **40** 339 (April) 1943. (c) Boyd, W. The Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1940, p. 159.

63 Reimann, Havens and Price.^{24f} Kneeland and Smetana.^{27b} Saphir.^{62b}

64 (a) Adams.^{13a} (b) McCordock and Smith.⁴²ⁿ (c) Schmitz.^{49c} (d) Gedgoud, J. L. The Diagnosis of Virus Pneumonitis in Infancy, *Nebraska M. J.* **28** 51 (Feb.) 1943.

65 Sabin, A. B. Toxoplasmic Encephalitis in Children, *J. A. M. A.* **116** 801 (March 3) 1941.

66 Peterson, O. L., and Finland, M. Modern Treatment of Pneumonia, *M. Clin. North America* **27**:1291 (Sept.) 1943.

cells⁷⁴ to 2,000 cells per cubic millimeter, 90 per cent of which are neutrophils, increase of cerebrospinal fluid protein⁷⁵ content and lowering of the blood serum albumin-globulin ratio^{27b}. The sedimentation rate is increased, especially toward the end of the disease. Van Ravenswaay and associates showed that for patients who are kept in bed until the sedimentation rate is 10 mm in one-half hour recurrences are fewer and the total time in bed per patient is less.^{40d} Helwig and Freis showed that the sedimentation rate in 1 case was increased but that this did not occur when the citrated blood was kept at body temperature.⁷⁶ In primary atypical pneumonia there is no hypoaminoacidemia, excess retention of sodium chloride and water in the acute stage or excess excretion of sodium chloride and water during convalescence, as in pneumococcal pneumonia.⁷⁷

Cold agglutinins appear during the acute stage (after the eighth to tenth day) of the disease,⁷⁸ and the height of the titer has no relationship to the severity of the disease or to the size of the pulmonary lesion. In a group of cases in Great Britain during the winter of 1942-1943 these agglutinins occurred in more than 90 per cent of the cases.^{78d} Difficulties in making the major cross matches as well as agglutination of cells in the red cell pipet due to cold agglutinins of these patients may be overcome by working with solutions and instruments at 37 C.⁷⁹ The urine is usually cloudy, has a few white cells in it occasionally and has a slight trace of albumin, as one would expect in toxic, febrile diseases. Glycosuria that cleared immediately has been reported.⁵ The serologic reactions have been reported as

73 (a) Green and Eldridge^{3a} (b) Reimann^{11b} (c) Sheppe, W. M., Osterman, A. L., Ahroon, C. R., and Zuflacht, J. J. Meningomyelitis. A Complication of Primary Atypical Pneumonia, *J. A. M. A.* **122** 1245 (Aug 28) 1943

74 (a) Green and Eldridge^{3a} (b) Reimann^{11b} (c) Sheppe, Osterman, Ahroon and Zuflacht^{73c} (d) Campbell, T. A., Strong, P. S., Grier, G. S., and Lutz, R. J. Primary Atypical Pneumonia. A Report of Two Hundred Cases at Fort Eustis, Virginia, *J. A. M. A.* **122** 723 (July 10) 1943

75 Owen⁵ Campbell, Strong, Grier and Lutz^{74d}

76 Helwig, F. C., and Freis, E. D. Cold Auto-hemagglutinins Following Atypical Pneumonia Producing the Clinical Picture of Acrocyanosis, *J. A. M. A.* **123** 626 (Nov 6) 1943

77 Emerson, K., Jr., Curnen, E. C., Mirick, G. S., and Ziegler, J. E. Chloride Metabolism and Plasma Amino Acid Levels in Primary Atypical Pneumonia, *J. Clin. Investigation* **22** 695 (Sept) 1943

78 (a) Peterson and Finland⁶⁶ (b) Horstmann, D. M., and Tatlock, H. Cold Agglutinins. A Diagnostic Aid in Certain Types of Primary Atypical Pneumonia, *J. A. M. A.* **122** 369 (June 5) 1943 (c) Turner, J. C. Development of Cold Agglutinins in Atypical Pneumonia, *Nature, London* **151** 419 (April 10) 1943 (d) Turner, J. C., and Jackson, E. B. Serological Specificity of an Auto-Antibody in Atypical Pneumonia, *Brit. J. Exper. Path.* **24** 121 (June) 1943

shifting⁸⁰ and as positive.⁸¹ Langille had a case in which the Kahn test gave a positive but the Eagle test a negative reaction, the serologic reaction became completely negative in two months.^{68b} A gold salt curve has been reported as 1122210000.³³ The serum in several cases gave a positive reaction to a Weil-Felix agglutination test.⁸² The Frei test has been reported to give positive results in some cases.^{24h} Agglutination of sheep cells has been reported in cases with negative serum reactions previously.⁸³ Electrocardiographic changes according to Kurtz are low voltage, deviation of the ST segments, flattening of the T waves, severe sinus arrhythmia, bradycardia and conduction disturbances. Deviation of the axis to the left has also been noted. Sinus arrhythmia and bradycardia may exist for several weeks or a few months after recovery, during this time the patient has a feeling of malaise.⁸⁴ One must rule out, electrocardiographically, coronary occlusion.⁸⁵

ROENTGEN FINDINGS

Roentgenographic evidence appears about one^{14a} to four⁸⁶ days after the onset of the disease. As early as 1934 Gallagher noted that roentgenograms show more than the physical changes would seem to justify.⁸⁷ This may be due to interstitial involvement of the lungs and possible lack of consolidation within the alveoli, or the area of consolidation or the involved alveoli may be sandwiched deeply between essentially normal pulmonary tissue. On the other hand, the patient may be extremely ill with the disease although the roentgen findings may be minimal or even absent.⁸⁸ In mild forms the roentgenogram may show only an increased

79 Dameshek, W. Cold Agglutinins in Acute Hemolytic Reactions in Association with Sulfonamide Medication and Infection, *J. A. M. A.* **123** 77 (Sept 11) 1943

80 Owen⁵ Kneeland and Smetana^{27b}

81 Green^{3a} Owen⁵

82 (a) McNaught, J. B. Virus Pneumonia. A Review of the Pathology, *California & West Med* **59** 220 (Oct) 1943 (b) Sachs, J. Recent Advances in Diagnosis and Treatment of Virus and Atypical Pneumonia, *New York State J. Med* **44** 485 (March 1) 1944

83 Shone and Passmore^{52b} Young, Storey and Redmond^{72c}

84 Kurtz, C. M. Personal communication to the author. This work is to be published at a later date.

85 Fuller, C. C., and Quinlan, J. W. Acute Pneumonitis and Pericarditis, *New England J. Med* **229** 399 (Sept 2) 1943

86 McCarthy, P. V. Primary Atypical Pneumonia of Unknown Etiology, *Radiology* **40** 344 (April) 1943

87 Gallagher, J. R. Bronchopneumonia in Adolescence, *Yale J. Biol. & Med* **7** 23 (Oct) 1934

88 Berryhill, Hedgpeth, Morgan, Stone and Smith^{14e} Cass⁴⁴ Schmitz^{49c} Levin, S. L. Primary Atypical

density in the costophrenic angle⁸⁹ or at the cardiophrenic angle^{19a}. Likewise there may be just a diffuse increased density of one lobe. One may notice only an increase in the pulmonic markings, resembling bronchitis. This is due to peribronchial and perivascular infiltration. The spread is via continuity and contiguity of tissue, and this process is responsible for the interbronchial cottony shadows. The lesions are usually found in the lower lobes. An entire lobe may be involved, in all probability because of the extension and coalescence of the cottony areas. The plate may resemble that seen in lobar pneumonia except that the shadow does not obscure the vascular or osseous markings^{3a}. There may at times be visceral pleural thickening that may also resemble lobar pneumonia⁹⁰. Inadequately treated pneumococcic pneumonia may show reticular markings that will not clear as rapidly as those seen in primary atypical pneumonia^{19a}. In other cases there may be a fan-shaped lesion in the hilus or less commonly in the periphery of the lung, or a lesion that spreads into one or both lungs. Patients with diffuse patchy involvement generally have a more prolonged course than those with a localized lesion⁵⁷. The clearing time may range from three²² to more than sixty-two days⁹¹. McCarthy suggested that patients be dismissed from the hospital only after the roentgenogram is relatively normal⁸⁶.

The extent of involvement of the parenchymal tissue is not always apparent. There may be continual changes for some days or weeks, such as extension or clearing. This mutation is of diagnostic value, especially in differentiating this disease from tuberculosis, thus differential diagnosis requires serial plates. At the Middlesex County Sanatorium plates are taken at intervals of two weeks before the diagnosis of tuberculosis is made⁹². Formation of pseudocavities in this pulmonary condition is also differentiated from tuberculosis by consecutive plates^{19a}. Thus serial roentgenograms should be taken for draftees before they are rejected because of possible tuberculosis. The hilar nodes are not so enlarged in early tuberculosis, and the striations extending to the hilus from the consolidated tuberculous

areas are more extensive than in primary atypical pneumonia^{19a}. There is little tendency in this disease to involve the pleura²². Bowen stated that at times there are residual fibrosis and incomplete reabsorption of the pulmonary lesion, this makes the differential diagnosis from tuberculosis even more difficult⁹³. Thus roentgenologically primary atypical pneumonia must be differentiated from acute bronchitis, bronchopneumonia, cancer, early pulmonary abscess, tuberculosis, pneumococcic pneumonia and acute bronchiectasis^{11a}.

DIAGNOSIS

Diagnosis can be made by (1) the roentgenograms, (2) the history, and the physical examination and (3) the therapeutic test with sulfonamide compounds and the processes of elimination, which are the least desirable methods of diagnosis. The results may be misleading in persons with inadequately treated or sulfonamide-resistant coccic pneumonia. This is particularly true of children with pneumonia⁹⁴.

The isolation of cold agglutinins (autohemagglutinins) is now suggested as an aid in diagnosis of certain types of primary atypical pneumonia⁹⁵.

DIFFERENTIAL DIAGNOSIS

Influenza is the most difficult condition to differentiate from the mild form and the early stages of this disease. The roentgenogram in influenza is not abnormal^{19a}. The marked inflammatory reaction in the pharynx⁹⁶ and the catarrhal symptoms of influenza⁵⁷ are absent in primary atypical pneumonia. Pain on rotation of the eyes as elicited in influenza is rarely present,⁴⁵ but aching of the eyes is not uncommon. The tenderness of the bones and the gastrocnemius muscle that may occur in influenza was not present in Longcope's cases^{14b}. The symptom of generalized muscular aches is more distressing in influenza, and the headache as atypical pneumonia progresses seems to be more disturbing⁹⁷. In

Pneumonia, Etiology Unknown. Report of Thirty-Five Cases, *M Bull Vet Admin* **20** 122 (Oct) 1943.

89 (a) Murray^{14a} (b) Duggan and Powers^{40b} (c) Scott, W G, and Jones, H L, Jr. Acute Pneumonitis, *Am J Roentgenol* **50** 444 (Oct) 1943.

90 Curtzweiler, F C, and Moore, B E. Primary Atypical Pneumonia of Unknown Etiology, *Radiology* **40** 347 (April) 1943.

91 Haight, W L, and Trolinger, J H. Primary Atypical Pneumonia, Etiology Unknown, *U S Nav M Bull* **41** 988 (July) 1943.

92 Davenport, L F. Atypical Pneumonias, *Bull New England M Center* **4** 17 (Feb) 1942.

93 Bowen, A. Acute Influenza Pneumonitis, *Am J Roentgenol* **34** 168 (Aug) 1935.

94 Finland, M. The Diagnosis of Virus and Bacterial Pneumonia in Children, *New England J Med* **229** 199 (July 29) 1943.

95 (a) Horstmann and Tatlock^{78b} (b) Peterson, O L, Ham, T H, and Finland, M. Cold Agglutinins (Autohemagglutinins) in Primary Atypical Pneumonia, *Science* **97** 167 (Feb 12) 1943. (c) Turner, J C, Nisnewitz, S, Jackson, E B, and Berney, R. Relation of Cold Agglutinins to Atypical Pneumonia, *Lancet* **1**:765 (June 19) 1943. (d) Meiklejohn, G. The Cold Agglutination Test in the Diagnosis of Primary Atypical Pneumonia, *Proc Soc Exper Biol & Med* **54** 181 (Nov) 1943.

96 Opie, E L. The Pathologic Anatomy of Influenza, *Arch Path* **5** 285 (Feb) 1928.

97 Field, H. Acute Respiratory Infections, Including Virus Pneumonia, *West Virginia M J* **40** 69 (March) 1944.

influenzal pneumonia there are early extreme (grayish) cyanosis⁹⁸ and dyspnea, increased respiratory rate, prostration and euphoria. This type of pneumonia is said to occur only during epidemics of influenza^{62c}.

Bronchopneumonia usually gives little trouble in the differential diagnosis. To the aged, in whom the onset of pneumonia is insidious and the fever and white cell count are low, sulfonamide compounds are justifiably given until one is certain that the patients have primary atypical pneumonia. Patients with bronchitis who have no history of allergy, previous colds or influenza should be examined carefully for possible primary atypical pneumonia⁵⁷. The hyperemia and generalized edema of the throat seen in the common cold are not present⁵⁷, however, hypertrophy of lymphoid follicles on the posterior pharyngeal wall is occasionally seen⁴⁶. Atypical pneumonia, like the lobar type, has been confused with acute appendicitis, and under such conditions appendixes have been removed.

Pneumococcal pneumonia does not produce a rise in the titer of cold agglutinins during the second and third weeks. Likewise, there is usually no significant change in the titer of cold agglutinins in advanced tuberculosis, during convalescence from sinusitis, in hemolytic streptococcal sore throat, or in the common cold. Rarely does the titer in a normal person exceed 1:16^{95c}.

The differential diagnosis includes lobar pneumonia, influenza, psittacosis, tuberculosis, bronchitis, bronchopneumonia, bronchiectasis, malaria, typhoid, undulant fever, tularemia, fungous diseases of the lungs, toxoplasmosis and pneumonia produced by measles, influenza, chickenpox, vaccinia and variola.

COMPLICATIONS

Although complications are uncommon, they are mentioned here in order that a fuller understanding of the disease may be had.

Kneeland and Smetana reported on a patient who had slightly elevated erythematous areas of skin that ranged up to almost 2 cm in diameter. This eruption occurred early, was generalized and was accompanied by a relapsing fever. The patient was stuporous, he had a stiff neck and a positive Babinski reaction on the left side. Another of their patients had severe polyarthritides with heat and swelling that did not respond to salicylates. There were also pericarditis and bilateral pleural effusion. This patient required four months of hospitalization and had a prolonged convalescence. Other complications were orthopnea, heart failure, urticaria, thrombo-

phlebitis, oliguria, gross hematuria, hypoproteinemia, meningism, coma and jaundice^{27b}. Longcope reported bilateral thrombi in the legs with pulmonary infarcts^{11b} and also occasional erythematous areas on the skin^{18d}. Allen reported otitis media, urticaria, acute maxillary sinusitis, peritonsillar abscess and even necrosis of the cervical nodes as complications⁹⁹. Reimann added a few cases of encephalitis and such signs and symptoms as positive Kernig's sign, ankle clonus, mental confusion and euphoria^{11b}. Cass and a number of others¹⁰⁰ have reported cases in which empyema occurred. Adams had a case of secondary infection of the lungs with a pneumococcus and another case of pulmonary abscesses^{13a}. McKinlay found on postmortem examination fresh cardiac lesions that were thought to have occurred during the course of primary atypical pneumonia. The valvular damage simulated the lesions of rheumatic fever^{36b}. Longcope¹² and Moore and his associates⁹⁸ reported deaths from this disease of patients who had had rheumatic endocarditis. Green reported dilatation of the heart, which regressed as the patient improved^{3a}. Other complications reported are ulceration of the soft palate, tonsillitis, streptococcal pharyngitis^{14a}, erythema multiforme¹⁰¹ with involvement of the mucous membrane, staphylococcal pneumonia, asthmatic breathing¹⁰², a continued productive cough suggesting bronchiectasis¹⁰³, massive hemoptysis¹⁰⁴, chronic pyelonephritis, acute focal hepatitis^{24f}, acute hemolytic anemia¹⁰⁵, pleurisy, spontaneous pneumothorax, eustachian pyosalpingitis, toxic myocarditis, acute cystitis, nephritis and infectious mononucleosis³⁷, conjunctivitis and stomatitis¹⁰⁶, nonspecific urethritis^{40d}, meningomyelitis^{73c}, facial palsy⁵, myelitis with resulting paralysis of the legs, and fractured ribs due to excessive strenuous coughing^{74d}. There may also be a late manifestation of acrocyanosis⁷⁶. Relighting of old tuberculous lesions has occurred¹⁰⁷. The bronchi may dilate, producing pseudobronchiectasis, they return to normal in about three months¹⁰⁸. Thus one must evaluate the immedi-

99 Allen, W. H. Acute Pneumonitis, *Ann Int Med* 10:441 (Oct) 1936.

100 Adams^{13a} Murray^{14a}

101 Markham, J. Acute Pneumonitis. An Atypical Bronchopneumonia of Virus Origin, *Canad M A J* 47:133 (Aug) 1942.

102 Longcope^{14b} Kneeland and Smetana^{27b}

103 Dingle and Finland^{11a} Van Ravenswaay and others^{40d}

104 Owen⁵ Van Ravenswaay and others^{40d}

105 Horstmann and Tatlock^{78b} Dameshek⁷⁹

106 Van Ravenswaay and others^{40d} Contratto⁷¹

107 Maxfield, J. R., Jr. Atypical Pneumonia with Leukopenia, *Texas State J Med* 35:340 (Sept) 1939.

98 Moore, G. B., Tannenbaum, A. J., and Smaha, T. G. Atypical Pneumonia in an Army Camp, *War Med* 2:615 (July) 1942.

ate history of men with bronchiectasis who are to be rejected by or discharged from the armed forces

TREATMENT

Harris and Stokes were able to reduce the incidence of infections of the upper respiratory tract in a pediatric ward with the use of vaporized propylene glycol¹⁰⁹ Although this aerosol does not destroy organisms afloat on particles of dust, it does destroy germs ejected into the air with a fine spray of moisture¹¹⁰ Perhaps this material could be used to prevent the spread of this and other diseases in Army camps, schools, theaters, hospital wards, etc The vapor is nonexplosive if kept at the concentrations required to sterilize air¹¹¹ Triethylene glycol is thought to be superior to propylene glycol¹¹²

Despite isolation the disease has been known to spread^{9b} Oxygen is indicated for patients with delirium, cyanosis, dyspnea and hyperpnea Epinephrine, ephedrine and helium and oxygen under pressure have been used for asthmatic breathing¹¹³ In cases of pulmonary collapse bronchoscopy is recommended¹¹⁴ Steam inhalation and codeine are used for the dry cough Expectorants and benzoin inhalants have been used, but Cass has stated that they may aggravate the cough⁴⁴ Longcope stated that the cough in severe cases is often refractory to codeine, and he recommended oxygen for its control^{18d} Codeine and ice caps are used for headaches Lumbar puncture has been performed for relief of severe headaches²¹ Because of marked sweating, diaphoretics such as salicylates, aminopyrine and acetophenetidin are to be avoided^{18c} On the other hand, when a patient has a high temperature and is not perspiring, the diaphoretics may

be comforting⁴⁴ They are indicated for generalized muscular aches, including backache A tight binder has been recommended for abdominal muscular pain^{18c} Fluids are usually forced In the event of excessive sweating a 3 per cent solution of sodium chloride and cortin has been given to replace the lost salt⁹⁸ Transfusions are indicated for secondary anemia and plasma for hypoproteinemia

The treatment of infants is essentially the same as that of adults The liberal use of fluids, however, is to be avoided, for they are poorly tolerated and seem to aggravate the dyspnea, cyanosis and cough^{13c} Postural drainage may be indicated with aspiration of the mucus from the nose and throat Thiamine hydrochloride and nicotinic acid have been used for treatment and prevention of delirium¹¹⁵

In general, most authorities agree that sulfonamide compounds are not indicated in treatment of this disease unless there is definite evidence that secondary infection is present or that such a complication may set in It may be stated that sulfonamide drugs given prior to the time the temperature drops in its biphasic curve may produce a false impression of a favorable response and thus seemingly justify continued drug therapy¹¹⁶ When the diagnosis is not definite it would seem justifiable to use the drugs, but only for forty-eight to seventy-two hours if there is no response Some workers have stated that while chemotherapy was being employed the patients' temperatures were occasionally reduced¹¹⁷ Shone used sulfapyridine with a resultant reduction in the temperature, and when administration of the drug was stopped, the patients had exacerbation of fever^{52b} This confirms the work of Beeson, who showed that sulfapyridine is an antipyretic¹¹⁸ Markham stated that sulfonamide drugs have no effect on the patients' temperatures, and that if their administration is stopped, the patients are spared nausea and malaise¹⁰¹ In addition, some of these drugs when given in full doses for a period may produce sensitivity to the drugs, acute hemolytic anemia¹¹⁹ or some other types of anemias, agranulocytosis, increased leukocytosis,¹²⁰ cold

108 Blades, B, and Dugan, D J Pseudo-Bronchiectasis Following Atypical Pneumonia, *Bull U S Army M Dept*, November 1943, no 70, p 60

109 Stokes, J, Jr, and Henle, W Prevention of Epidemic Influenza, *J A M A* **120** 16 (Sept 5) 1942

110 Puck, T T, Robertson, O H, and Lemon, H M The Bactericidal Action of Propylene Glycol Vapor on Micro-Organisms Suspended in Air The Influence of Various Factors on the Activity of the Vapor, *J Exper Med* **78** 387 (Nov) 1943

111 Bigg, E, Jennings, B H, and Fried, S Inflammability Characteristics of Propylene Glycol and Triethylene Glycol in Liquid and Vapor Forms, *Am J M Sc* **207** 370 (March) 1944

112 Robertson, O H, Puck, T T, Lemon, H M, and Loosh, C G The Lethal Effect of Triethylene Glycol on Air-Borne Bacteria and Influenza Virus, *Science* **97** 142 (Feb 5) 1943 Bigg, E, Jennings, B H, and Fried, S The Use of Glycol Vapors for Bacterial Control of Large Spaces, *Am J M Sc* **207** 361 (March) 1944

113 Kneeland and Smetana^{27b} Barach, A L Physiologically Directed Therapy in Pneumonia, *Ann Int Med* **17** 812 (Nov) 1942

114 Lincoln, E M, Smith, C H, and Kirmse, T W Subacute Pneumonia in Children, *J Pediat* **16** 1 (Jan) 1940

115 Fulghum, C B Virus Pneumonia, *J M A Georgia* **32** 317 (Oct) 1943

116 Christian, H A, in discussion on Longcope^{18d}

117 Allen and Baird^{3b} Owen⁵

118 Beeson, P B, and Janeway, C A Antipyretic Action of Sulfapyridine, *Am J M Sc* **200** 632 (Nov) 1940

119 Boyer, N H Acute Hemolytic Anemia Following Sulfadiazine Report of a Case, *New England J Med* **228** 566 (May 6) 1943

120 Spink, W W Sulfonamide and Related Compounds in General Practice, Chicago, The Year Book Publishers, Inc, 1943

agglutinins⁷⁹ and anorexia. There is no therapeutic response, and the patients often state that they feel better after administration of the drug is stopped. Moreover, these drugs may reduce aviators' ceiling zero^{89c} as well as impair judgment.¹²¹ Cold agglutinins plus sulfonamide drugs may be responsible for acute hemolytic anemia.⁷⁹ Furthermore, Royster expressed the opinion that chemotherapy prolongs the disease and seems to make patients worse.¹²² Suttentfield stated the view that withdrawal of the sulfonamide drugs definitely saved several patients' lives.^{17b} Treatment with sulfonamide drugs alone has resulted in a mortality rate of 0.2 per cent.¹²³ Penicillin has been unsatisfactory in the treatment of this disease.¹²⁴

Transfusions of whole blood have been given with the specific hope of imparting immune bodies to patients. Adams and co-workers reported administration of 30 cc of normal adult blood to 7 babies early in the course of the disease and to 7 others before they had become ill. No deaths occurred in this group of 14 infants.^{13c} Flexner used convalescent whole blood with good results, as others have done.¹²⁵ On the other hand, Young gave plasma and whole blood from convalescent donors to 12 patients without any definite response.^{72c} Immune bodies have been proved to exist in the blood of convalescent patients.¹²⁶ The titer of the antibodies during convalescence is greater than that during the acute phase.^{6e} Roentgen ray treatment has been said to abate the cough, bring the temperature down within forty-eight¹²⁷ to seventy-two hours and clear the roentgenogram.¹²⁸ Naval officers

stated that they felt they had reduced the febrile period, the number of days of resolution and the total number of days of illness, roughly speaking, by one half through roentgen ray treatment.^{15b}

PROGNOSIS

Prognosis in general for the majority of cases is good. This disease in its severe form, superimposed on an already damaged heart, will warrant a guarded prognosis. A number of deaths have been reported in the United States.¹²⁹ Undoubtedly reports of some cases that terminated fatally have not appeared in the literature. In 1,862 cases that occurred in an army camp a mortality rate of 0.26 per cent was reported.^{40d} Among civilians the rate is estimated to be 2.4 per cent.⁵

CONCLUSIONS

Treatment is symptomatic. Sulfonamide drugs may be detrimental, and penicillin seems to be without results. The administration of oxygen under positive pressure in severe pneumonia may be life saving. With the use of roentgen rays and convalescent serum and with the sedimentation rate as a guide to the time of dismissal, the period of hospitalization may be reduced.

In rejecting persons for the armed forces and in discharging military personnel because of tuberculosis or bronchiectasis, one must consider the possibility of recent primary atypical pneumonia.

128 Uhlmann, E, in discussion on Hufford and Applebaum^{125g}; Oppenheimer, A. Roentgen Therapy of "Virus" Pneumonia, *Am J Roentgenol* **49** 635 (May) 1943.

129 Lusk and Lewis^{2b}; Smiley⁴; Eaton and Corey^{6e}; Meiklejohn, Beck and Eaton^{6j}; Eaton, Beck and Pearson⁸; Reimann^{11b}; Longcope¹²; Adams, Green, Evans and Beach^{13c}; Berryhill, Hedgpeth, Morgan, Stone and Smith^{14e}; Dingle and others²²; Kneeland and Smetana^{27b}; Solomon and Kalkstein^{28a}; Thomas^{28b}; Thomas, Mirick, Curmen, Ziegler and Horsfall²⁹; McKinlay, Lange and Boehr^{30b}; Van Ravenswaay and others^{40d}; Goodpasture, Auerbach, Swanson and Cotter^{42b}; Cass⁴⁴; Schmitz^{40c}; Needles and Gilbert⁵³; Gedgoud^{64d}; McKinlay and Cowan⁶⁷; Campbell, Strong, Grier and Lutz^{74d}; Horstmann and Tatlock^{78b}; McNaught^{82a}; Sachs^{82b}; McCarthy⁸⁰; Moore, Tannenbaum and Smaha⁹⁸; Bayne-Jones^{125e}; Hufford and Applebaum^{125g}; Oppenheimer^{127b}; Hornibrook, J W, and Nelson, K R. An Institutional Outbreak of Pneumonitis. Epidemiological and Clinical Studies, *Pub Health Rep* **55** 1936 (Oct 25) 1940; Finland, M, in discussion on Longcope^{18d}; Rothenberg, R C. Atypical (Virus) Pneumonia. A Case with Autopsy Report, *Cincinnati J Med* **24** 152 (June) 1943; Deaths of Physicians in 1943, editorial, *J A M A* **124** 36 (Jan 1) 1944; Death Notices, editorial, *ibid* **124** 663 (March 4) 1944; Stats, D, and Wasserman, L R. Cold Hemagglutination. An Interpretive Review, *Medicine* **22** 363 (Dec) 1943.

121 Mental Confusion from the Sulfonamides, editorial, *J A M A* **119** 1431 (Aug 22) 1942.

122 Royster, C, in discussion on Berryhill and others^{14e}.

123 Janeway, C A. The Sulfonamides. Their Clinical Use, *New England J Med* **227** 1029 (Dec 31) 1942.

124 Herrell, W E. The Clinical Use of Penicillin, an Antibacterial Agent of Biologic Origin, *J A M A* **124** 622 (March 4) 1944.

125 (a) Adams, Green, Evans and Beach^{13c}; (b) Kneeland and Smetana^{27b}; (c) Goodman^{40c}; (d) Maxfield¹⁰⁷; (e) Bayne-Jones, S. Virus Pneumonia, *Connecticut M J* **4** 258 (May) 1940; (f) Flexner, M, and Garson, M L. Virus Pneumonia. Treatment with Convalescent Blood, *Kentucky M J* **41** 5 (Jan) 1943; (g) Hufford, C E, and Applebaum, A A. Atypical Pneumonia of Probable Virus Origin, *Radiology* **40** 351 (April) 1943.

126 Eaton, Beck and Pearson⁸; Weir, J M, and Horsfall, F L, Jr. The Recovery from Patients with Acute Pneumonitis of a Virus Causing Pneumonia in the Mongoose, *J Exper Med* **72** 595 (Nov) 1940.

127 (a) Offutt, V D. Diagnosis and Treatment of Primary Atypical Pneumonia, *South Med & Surg* **106** 5 (Jan) 1944; (b) Oppenheimer, A. Roentgen Therapy of Interstitial Pneumonia, *J Pediat* **23** 534 (Nov) 1943.

EFFECTS OF COLD AIR ON THE AIR PASSAGES AND LUNGS

AN EXPERIMENTAL INVESTIGATION

ALAN R MORITZ, M D, AND JAMES R WEISIGER, P H D

BOSTON

The absence of reliable information concerning the effects of cold air on the air passages and the lungs and concerning the rate at which inhaled cold air is warmed within the body led to the undertaking of this investigation on dogs

In order to observe the pathologic and physiologic changes resulting from the inhalation of cold air independent of any indirect or secondary effects that might result from the simultaneous chilling of the surface of the body, the air was brought into the mouth and throat through a vacuum-jacketed (Dewar) cannula, and the animals were not otherwise exposed to cold. Care was exercised to see that the dogs had no source of air for respiration other than that which had passed through a cooling system

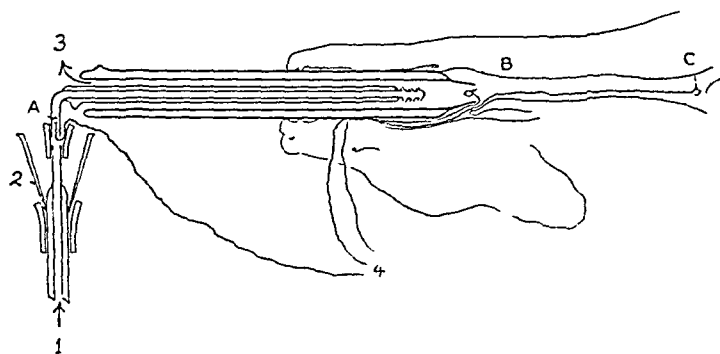


Fig 1—Diagrammatic representation of the cannula through which cold air was brought to the larynx, 1, source of cold air which had been chilled by circulation through a bath of liquid nitrogen and alcohol, 2, glass flange filled with liquid nitrogen to prevent warming of the noninsulated segment of the conduction system, 3, outer compartment of the transoral cannula through which exhaled air was discharged, 4, thermocouple leads to the potentiometer and to the galvanometer, A, thermocouple in the cold air stream before entering the inner compartment of the cannula, B, thermocouple in the laryngeal opening of the cannula, C, thermocouple at the bifurcation of the trachea

The air was chilled by passage through a radiator (converted automobile heater) which was immersed in a large Dewar container filled with a mixture of liquid nitrogen and alcohol. The rate of flow was maintained at 30 liters per minute by means of a flowmeter inter-

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The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University

Dr F C Henriques Jr aided in adaptation and calibration of the recording instruments used in this investigation

posed between the compressed air line and the cooling mixture. To prevent blockade of the cooling system by formation of ice it was necessary to pass the air through a trap before it entered the radiator. This trap, which was immersed in the nitrogen-alcohol mixture, consisted of a tube 25 cm long and 2 cm in diameter. After leaving the flowmeter and before entering the radiator the air passed through this tube, where the moisture contained by it was condensed and frozen

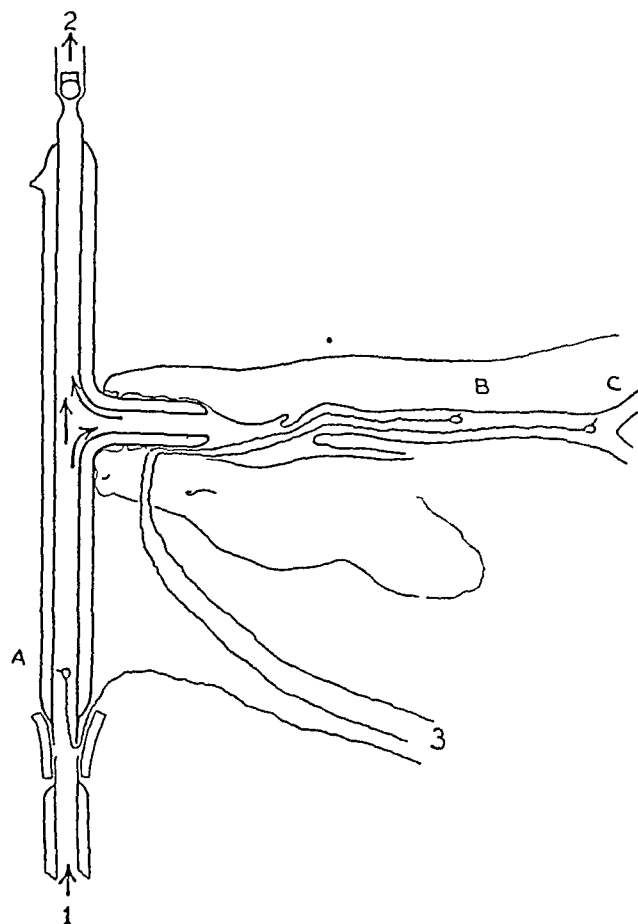


Fig 2—Diagrammatic representation of the cannula through which cold air was brought to the midportion of the mouth 1, source of cold air which had been chilled by circulation through a bath of liquid nitrogen and alcohol, 2, outlet for exhaled air, 3, thermocouple leads to the potentiometer and to the galvanometer, A, thermocouple in the cold air stream before entering the cannula, B, thermocouple in the midportion of the trachea, C, thermocouple at the bifurcation of the trachea

After leaving the radiator the air was conducted through a vacuum-jacketed tube to the animal's mouth. In one series of animals the cold air was conveyed directly to the laryngeal orifice (fig 1), and in another series it was conveyed to a point about midway between the front teeth and the larynx (fig 2). In each instance the transoral cannula was constructed on the

Dewar principle in order to reduce to a minimum the conduction of heat through its wall

The laryngeal cannula (fig 1) used in the first series of animals was constructed in such a way that the cold air was brought through an inner compartment to the laryngeal orifice for inhalation and was exhaled through an outer compartment. The inhalation of warm air through the outer compartment was prevented by maintaining a rapid (30 liters per minute) flow of air in the reverse direction. In experiments in which this cannula was used, it was necessary to interrupt the cold air stream at frequent intervals (about once every five minutes) to prevent blockade of the outer compartment and insulation of the laryngeal thermocouple by ice formed by the condensation and congelation of moisture from the exhaled air.

The midoral cannula (fig 2) which was used in the second series of experiments was constructed in such a manner that both the cold air for inhalation and the warm exhaled air passed in and out of the mouth through the same compartment. Between respirations the air contained by the intraoral element of the cannula was relatively stagnant. During inspiration cold air was drawn out of the main air stream which was passing

with a General Electric recording galvanometer having a period of 0.2 second. Rectal temperatures before, during and after inhalation of cold were determined by a mercury thermometer.

In the first 3 experiments ethyl carbamate was used as an anesthetic agent, and in all 3 instances the animals died between two and six hours after induction of anesthesia. In subsequent experiments anesthesia was induced by intravenous injections of phenobarbital sodium.

In 2 experiments, 597 and 598, a continuous record of the rate and amplitude of respiratory excursions as well as of heart rate and blood pressure were made. In 2 experiments, 592B and 638, samples of venous blood were taken before, during and after inhalation of cold for determination of oxygen, carbon dioxide, pH, cell volume, red blood cell count, white blood cell count and differential blood count.

RESULTS OF EXPERIMENTS

As indicated in table 1, the animals breathed air that emerged from the cooling system at a

TABLE 1—Ranges of Temperature of Air Inhaled

Experiment Number	Site of Primary Impact of Cold Air	Length of Time That Animal Breathed Cold Air, Min	Average External Temperature of Air Stream, C	Temperature of Air at Different Levels Between Mouth and Lungs, C				
				Larynx, Lowest Inspiratory Nadir	Midtrachea (10 Cm Below Larynx)		Lower End of Trachea (22 Cm Below Larynx)	
					Lowest Inspiratory Nadir	Average Expiratory Peak	Lowest Inspiratory Nadir	Average Expiratory Peak
593	Intralaryngeal	20	-100	-40			+30	+39
676	Intralaryngeal	20	-100	-40			-27	+39
598	Intralaryngeal	20	-100	-30			+18	+39
592A	Intralaryngeal	40	-100	-28			+23	+37
635A	Intralaryngeal	40	-100	-50			+23	+38
597	Intralaryngeal	20	-100	-37			+25	+39
592B	Midoral	5	+25				+38	+39
		48	-100				+20	+37
638	Midoral	5	+20		+30	+37	+37	+39
		6	-40		+27	+37	+27	+39
		17	-65		+23	+33	+26	+37
		42	-100		+18	+35	+23	+37
635B	Midoral	133	-100		+18	+36	+21	+38

through the vertical element of the cannula. During expiration the warm exhaled air joined the cold air stream and was discharged with it through the upper orifice of the vertical element. A ball valve at the upper orifice of the vertical element prevented the ingress of warm air during inspiration. Actually the rate of flow of cold air through the vertical element was sufficient to prevent inspiration of warm air even if the ball valve had not been there.

Sensitive copper-constantan thermocouples constructed of 40 gage wire were introduced into the air stream at the various locations indicated in figures 1 and 2. These thermocouples either were provided with rigid supports or were enclosed in wire cages so as to insure their being free in the air stream and having no contact with the wall of the airway. The thermocouples measuring the temperature of the external air stream were not exposed to sudden changes in temperature and were therefore connected with an ordinary potentiometer. The thermocouples which were exposed to the respiratory fluctuations in temperature were connected in the first 3 experiments with a Mohl galvanometer having a period of 0.16 second and in subsequent experiments

temperature of approximately -100 C for periods ranging between twenty and one hundred and thirty-three minutes.

In the first series of experiments (cannula 1) the temperature of the inhaled air was measured at the larynx and at the bifurcation of the trachea. Despite the fact that the air had been conducted from the cooling system to the larynx through a vacuum-jacketed tube, its temperature had been raised from -100 to between -50 and -28 C by the time it reached the larynx. The coldest inspiratory nadir observed in any animal at the orifice of the laryngeal cannula was -50 C. In 1 animal (592A), -28 C was the lowest temperature recorded at the laryngeal orifice. It was characteristic that the lowest inspiratory temperatures recorded by the laryngeal thermocouple occurred during the first

two or three minutes after the flow of the cold air stream was started. Subsequent condensation and freezing of moisture from the exhaled air in the laryngeal orifice of the cannula was indicated first by lack of responsiveness of the thermocouple and later by actual obstruction to the flow of air.

By the time that the inhaled cold air reached the bifurcation of the trachea it had been warmed to a level well above freezing. Thus the lowest inspiratory nadir registered by the thermocouple at the bifurcation of the trachea was $+18^{\circ}\text{C}$. This occurred in an animal whose lowest inspiratory nadir at the larynx was -30°C . It is of interest that in another animal (593) in which repeated laryngeal inspiratory nadirs of -40°C

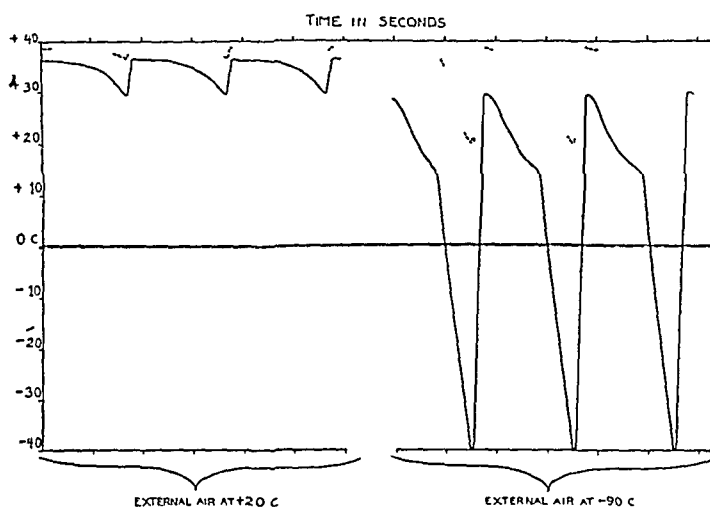


Fig. 3—Changes in temperature in the upper and lower portions of the trachea of a dog during the inhalation of warm ($+20^{\circ}\text{C}$) and cold (-90°C) air. Dotted line indicates temperature changes at bifurcation of trachea, solid line, temperature changes in laryngeal orifice of cannula.

were observed the temperature at the bifurcation of the trachea was never observed to drop below $+30^{\circ}\text{C}$. The slightness of the fluctuations in temperature recorded by the tracheal thermocouple in this animal may have been due to early plugging of the interstices of the guard cage by mucus. In all of this group of animals the air leaving the lungs was within 1 or 2 degrees of normal. Differences this small were not considered to be significant in view of the fact that they lay within the tolerance of the recording instruments.

In the second series of experiments shown in table 1 the cannula terminated about halfway between the front teeth and the larynx. In these experiments the animal's nose and mouth were bandaged with sheet rubber in such a way that no air could pass into or out of the lungs except by way of the cannula. It had been anticipated that in these experiments the

air would be warmer at the bifurcation of the trachea than it had been in the first series of animals. Despite the fact that air inhaled through this cannula must have been warmed to some extent by the back of the mouth before it reached the larynx, the inspiratory nadirs at the bifurcation of the trachea did not differ significantly from those observed in the first series of experiments.

Characteristic segments of the temperature changes recorded by the laryngeal and deep tracheal thermocouples during the breathing of warm and cold air are shown in figure 3. These examples were selected from the galvanometer recording of experiment 635A, in which the transoral cannula shown in figure 1 was used. In the original record the readings from the two thermocouples were recorded alternately rather than simultaneously.

When air at room temperature ($+20^{\circ}\text{C}$) was breathed, thermal fluctuations in the lower part of the trachea were perceptible only during the first few minutes. Later when the wall of the cannula had been warmed by contact with the oral mucosa and the exhaled air, the inspiratory depressions in temperature in the trachea became imperceptible except when abnormally deep breathing was stimulated by the mixture of carbon dioxide with the entering air stream.

When cold air (-100°C in the external segment of the cannula) was breathed, the differences between the inspiratory nadirs in the larynx and in the deep trachea became much more pronounced. Although the air temperature in the laryngeal orifice of the cannula (fig. 3) fell to -40°C , the air had been warmed to approximately $+20^{\circ}\text{C}$ by the time it reached the bifurcation of the trachea. The lowest air temperature in each situation was registered at the end of inspiration and the highest at the end of expiration. A noteworthy characteristic of the intralaryngeal inspiratory nadir is the shortness of the time during which the mucous membrane was exposed to a freezing temperature. For a period lasting approximately half a second during the latter part of each inspiration the air temperature in the larynx fell below 0°C . Immediately before and after such nadir the temperature was well above freezing. It appears that the breathing of cold air may cause a momentary exposure of the mucosa of the larynx and upper trachea to a freezing temperature but that the temperature at the bifurcation of the trachea is not likely to approach a cell-killing level of coldness at any time.

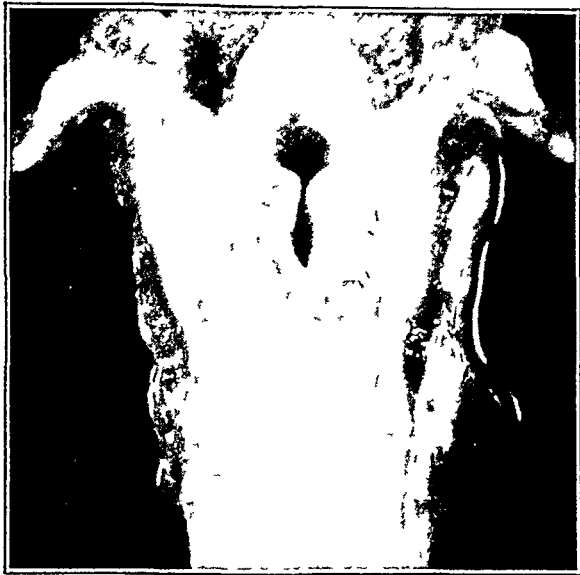


Fig 4—Obstructive edema of the pharynx and larynx due to prolonged direct exposure to cold (experiment 593)

ferential count It should be noted, however, that in no instance were the observations continued later than one hour after the animals' exposure to cold

So far as the clinical behavior of the animals was concerned, the only observable ill effect of the inhalation of the cold air was early hyperactivity of the mucous glands of the upper respiratory tract, with coughing and hoarseness of some of the animals during the first twenty-four hours All animals permitted to survive twenty-four hours or longer were lively, happy and not significantly disturbed by the experimental procedure

Postmortem pathologic studies (table 2) were made of 7 animals after postexposure intervals ranging between two and a half and forty hours In the case of the two and a half hour recovery period (593), the animal did not regain con-

TABLE 2—Clinical and Pathologic Observations

Experiment Number	Clinical Behavior After Inhalation of Cold Air	Postexposure Period	Principal Pathologic Changes
593	Obstructive edema of pharynx and larynx *	2½ hours	Obstructive edema of pharynx and laryngeal orifice
626	Excessive secretion of mucus from upper air passages	4 hours	Catarrhal sublaryngeal tracheitis, patchy atelectasis and emphysema
598A	Excessive secretion of mucus from upper air passages	5 hours	Catarrhal and membranous sublaryngeal tracheitis, patchy atelectasis and emphysema
592A	Excessive secretion of mucus for 12 hours, hoarse for 2 days, normal after second day	Survival experiment	Not determined
635A	Excessive secretion of mucus for 12 hours, hoarse for 2 days, normal after second day	Survival experiment	Not determined
597	Excessive secretion of mucus for 12 hours	12 hours	Catarrhal sublaryngeal tracheitis, patchy atelectasis and emphysema
592B	Normal	24 hours	Severe catarrhal laryngitis and sublaryngeal tracheitis, patchy atelectasis and emphysema
638	Excessive secretion of mucus for 12 hours, hoarse but otherwise normal	24 hours	Severe catarrhal and membranous sublaryngeal tracheitis, patchy atelectasis and emphysema with focal pneumonitis
535B	Excessive secretion of mucus, hoarse for 24 hours, normal after second day	40 hours	Mild sublaryngeal tracheitis, no abnormality of lungs

* Projecting 1.5 cm. beyond the vacuum jacket, the laryngeal end of the cannula had a solid glass wall. In experiment 593 the mucosa of the pharynx and larynx was in direct contact with this cold segment of glass. In subsequent experiments the tip of the cannula was wrapped with insulating material to reduce heat transfer at this site.

In no animal was a drop in rectal temperature observed during or after the inhalation of cold air

In neither of the 2 animals (597 and 598) for which kymographic recording of blood pressure and respiration was made was any striking change observed. There occurred an evanescent rise in systolic pressure and a slight increase in the rate and amplitude of the respiratory excursions of the thorax.

In neither of the 2 animals (592B and 638) from which samples of venous (femoral) blood were taken before, during and immediately after inhalation of cold air were significant disturbances observed in the oxygen or carbon dioxide saturation, the p_{H} , the cell volume, the red blood cell count, the white blood cell count or the dif-

ferential count. The animal died as a result of obstructive edema of the pharynx and larynx (fig 4). The edema developed rapidly, and although the obstruction was recognized and relieved by intubation approximately two hours after exposure, the animal was already anoxic beyond recovery. As previously indicated, the edema in this animal was caused by direct contact of the cold tip of the laryngeal cannula with the adjacent tissues. Obstructive edema was not observed in any of the succeeding experiments, in which the tip of the cannula was wrapped with insulating material. In this animal (593), the mucous membrane of the pharynx adjacent to the larynx had been in continuous contact with cold glass for twenty minutes. Wherever mucosal attachments permitted the

accumulation of interstitial fluid there was massive edema (fig 5). Although the animal died two and a half hours after exposure to cold, widespread necrosis of the glandular epi-

situations it was elevated by subepithelial collections of free fluid in the form of large and small vesicles. The subjacent tissues were hyperemic, hemorrhagic and sparsely infiltrated by poly-

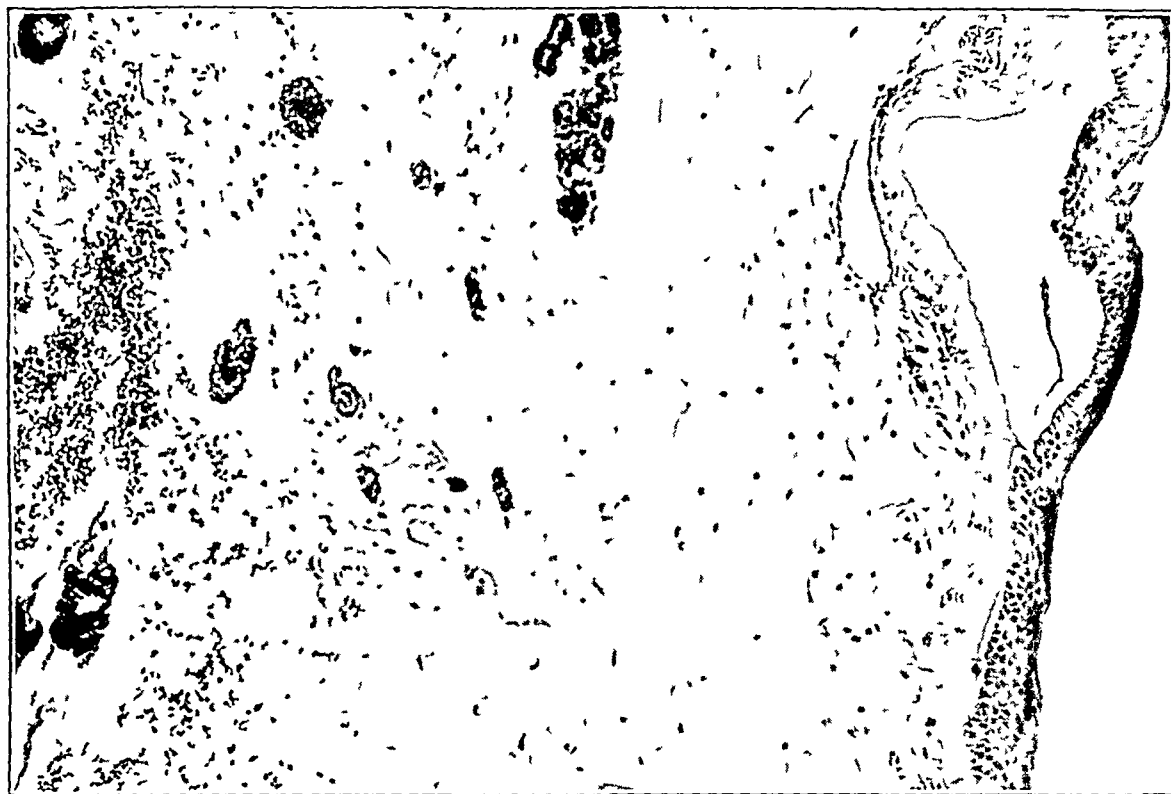


Fig 5—Photomicrograph showing hemorrhagic edema of the pharyngeal mucosa caused by direct exposure to cold (experiment 593) Magnification $\times 100$



Fig 6—Photomicrograph showing catarrhal inflammation of the mucous membrane of the upper portion of the trachea four hours after inhalation of cold air (experiment 626) Magnification $\times 100$

thelium and muscle of the pharynx had occurred. The stratified epithelium covering the surface appeared intact and showed remarkably little cytologic evidence of injury. In some

morphonuclear leukocytes. No thrombosis was observed. Other than hyperemia through its upper third, the tracheal mucosa showed no significant abnormality. The lungs were normal.

Between four and twelve hours after exposure there was more definite evidence of tracheitis. In the animals killed at this time there was some edema of the mucous membrane of the ventricular recesses of the larynx. Throughout the larynx and trachea there was evidence of excessive secretion of mucus (fig 6). Occasional patches of desquamated or elevated mucosal epithelium were encountered in the first 10 cm of the trachea. Scattered throughout all lobes of both lungs there were small platelike zones of atelectasis interspersed with subpleural foci of emphysema.

In both animals killed twenty-four hours after exposure to cold there was more extensive

mal was the amount of atelectasis great enough to interfere significantly with the respiratory exchange. In 1 animal (638) occasional collections of polymorphonuclear leukocytes were present in the alveoli and bronchioles of some of the atelectatic foci. Bacteria were not recognized microscopically.

The animal (635B) which had the longest and most severe exposure to cold was killed after a recovery period of forty hours. At the time the animal was killed its behavior was entirely normal, and postmortem examination disclosed less severe pathologic changes than had been observed in any of the previous animals. There was some residual tracheitis, as indicated by a



Fig 7—Photomicrograph showing severe sublaryngeal tracheitis twenty-four hours after inhalation of cold air (experiment 638). Magnification $\times 100$.

damage of the superficial epithelium of the larynx and sublaryngeal portion of the trachea. There was nonobstructive edema of the mucosa lining the ventricular recesses. Patches of membrane composed of tenacious mucus and desquamated epithelial cells were adherent to the mucosa of the larynx and upper part of the trachea (fig 7). In neither animal was there any significant gross or microscopic abnormality of the lower portion of the trachea or of the primary bronchi. Occasional small plugs of mucus mixed with desquamated epithelial cells were found in some of the smaller bronchi. The distribution of atelectasis and emphysema was similar to that described in preceding animals. In neither ani-

mild exudative reaction. There was no longer any evidence of excessive secretion of mucus, and whatever atelectasis and emphysema may have been present during the first twenty-four hours had now disappeared. No abnormality of the lungs was recognized microscopically.

Microscopic examination of the respiratory tracts of these animals at varying times after exposure to cold disclosed certain differences in the susceptibility of mucosal epithelium to thermal injury. The stratified epithelium of the mouth and, to a lesser extent, that of the pharynx and larynx were less susceptible to injury by cold than was the columnar epithelium of the upper portion of the trachea. In no

instance was there evidence of epithelial injury of the mouth, despite the fact that in the second series (fig 2) the primary impact of the cold air occurred in the midoral region. With the exception of animal 593 (noninsulated cannula) there was no subject in which necrosis of the laryngeal mucosa could be ascribed to thermal injury. Although the temperature to which the upper tracheal mucosa was exposed was undoubtedly lower than that to which the back of the mouth and larynx were exposed, there were several instances in which extensive epithelial destruction was observed in the former situation.

COMMENT

The inhalation of extremely cold air by dogs for periods ranging between twenty and one hundred and thirty-three minutes caused a catarrhal, and in some instances a membranous, tracheitis but failed to produce significant injury of the lower air passages or lungs. The temperature of air taken into a transoral cannula at -100°C rose to between -50 and -28 by the time it reached the larynx and between $+18$ and $+30^{\circ}\text{C}$ by the time it reached the lungs.

The results of this experimental investigation invite a consideration of the circumstances in which the exposure of living tissue to cold may result in cellular injury and in death. So far as *in vitro* observations are concerned, it has been shown both by Lambert¹ and by Fischer² that chilling is not likely to cause primary cellular injury unless the fall in tissue temperature is such that cells are disrupted by the formation of ice crystals. Similar conclusions were reached by Lewis³ from experiments performed *in vivo* on human skin. That intracellular congelation is not always prerequisite to injury by cold may be inferred from recent studies of immersion foot⁴. In this type of injury ischemic necrosis of an extremity, presumably due to the thermally induced neurocirculatory disturbances, may follow prolonged exposure to wetness and cold even though the tissue is at no time frozen.

Thus it appears that tissue may sustain primary injury if it is frozen or secondary injury without freezing if the exposure to cold is long enough to lead to a persistent disturbance in circulation.

When account is taken of the extremely low heat capacity of dry air, the nonoccurrence of primary pulmonary injury following the breathing of cold air is in no sense surprising. Volume for volume, water in a liquid state liberates about four thousand times as much heat energy for each degree it cools as does air. Thus, since water and protoplasm have about the same heat capacity, the number of calories required to raise 500 cc of air from an inhalation temperature of -40°C to an exhalation temperature of $+40^{\circ}\text{C}$ would be furnished by the heat given off by about 1 Gm of tissue, incident to a drop of 10 degrees in its temperature. Actually the number of calories lost by the respiratory mucosa incident to the warming of 500 cc of air under such conditions would probably be greater than 10, because the air would be relatively dry when inhaled and saturated with moisture when exhaled. The additional heat loss by the mucous membrane incident to the vaporization of this amount of moisture would bring the total deficit in such circumstances to approximately 20 calories per respiration. In consideration of the fact that these 20 calories could be supplied by the cooling of 1 Gm of tissue by approximately 20 degrees centigrade, no great amount of primary pulmonary injury due to the inhalation of cold air is to be expected.

The extent to which the evidence provided by these experiments can be applied to man should be considered. It is a fact that the trachea of a dog is long and narrow compared with that of man. It cannot be stated that because inhaled air is warmed from -50 at the larynx to $+23$ at the bifurcation of the trachea in the dog the same degree of warming would occur in man. It does seem likely, however, that these anatomic differences in dog and man would be more than offset by the fact that the cold air was conducted directly to the larynx of the dog by means of an insulated cannula, whereas in nonexperimental conditions man would have the added protection of his oral or nasal mucosa. It is also a fact that the rate of heat loss by the air passages would be augmented by rapid or deep breathing. Even if the rate were doubled or tripled, the total would not be impressive as a cause of direct pulmonary injury.

Although it may be inferred from these experimental results that intrapulmonic air temperatures much lower than $+20^{\circ}\text{C}$ are not likely to occur in man in nonexperimental conditions, nothing is known regarding the relative susceptibilities of man and dog to reflex circulatory or other disturbances which may occur in such circumstances. However, there was no indica-

¹ Lambert, R. A. *J. Exper. Med.* **18** 406, 1913.

² Fischer, A. *Arch. f. exper. Zellforsch.* **2**:303, 1926.

³ Lewis, T. *Brit. M. J.* **2** 795, 1941.

⁴ Blackwood, W. *Brit. J. Surg.* **31** 329, 1944.
White, J. C., and Warren, S. *Causes of Pain in Feet After Prolonged Immersion in Cold Water*, *War Med* **5** 6 (Jan) 1944.

tion, so far as the dog is concerned, of any local or general reflex disturbance caused by the inhalation of cold air. No attempt was made during this investigation to determine the extent to which the chilling of the upper respiratory mucosa may have altered its resistance to bacterial invasion.

A recent report by Smith⁵ calls attention to a syndrome of pain in the chest, cough, hemoptysis, patchy pulmonary consolidation and fever seen occasionally in flying personnel after high altitude missions in which intensely cold air was breathed. No pathologic studies of the condition are available. Smith stated that recovery generally occurred between ten days and two weeks after exposure.

On a basis of the experiments with animals reported here it is a fair inference that the disturbances described by Smith were due to an acute thermally induced hemorrhagic tracheitis with a certain amount of secondary atelectasis and pneumonitis probably caused by the aspiration of masses of mucus and desquamated tracheal mucosa. It is reasonable to believe that persons who have sustained such injury may be rendered more than normally susceptible to infection of the respiratory tract.

That man can breathe extremely cold air without sustaining pulmonary injury is indicated by a recent case at the Valley Forge Hospital.⁶ In November 1943, an aviator, while on duty in a gun turret, was wounded by a high explosive missile which also destroyed most of his protection against the cold air. For a period of about three hours he was exposed head foremost to a stream of air moving at the rate of 160 miles (258 kilometers) per hour and having a temperature of approximately -50°C . When he was admitted to the hospital, his face and fingers were frozen. Approximately six hours after his admission an obstructive edema of the mucous membranes of his mouth, nose and pharynx developed. An airway was established by means of a tracheotomy. He subsequently lost his fingers and much of the soft tissue of his face as a result of freezing. Despite an exposure to cold that led to an obstructive edema of his external respiratory passages, there was at no time evidence of injury to his bronchi or lungs, and he made an uneventful convalescence as far as pulmonary complications were concerned.

SUMMARY

In this investigation dogs were caused to breathe extremely cold air for periods ranging between twenty and one hundred and thirty-three minutes. The rate at which air was warmed within the body was measured by means of appropriately placed thermocouples. The air was delivered to the larynx at temperatures which ranged between -50°C and -28°C , and in no instance were temperature recordings lower than $+18^{\circ}\text{C}$ observed at the bifurcation of the trachea.

The inhalation of cold air in circumstances such that intralaryngeal inspiratory nadirs as low as or lower than -30°C were reached⁷ resulted in the development of a localized sub-laryngeal tracheitis. In some animals the disturbance was limited to unusual activity on the part of the mucous secreting glands, and in others there was focal destruction of the superficial epithelium. In no instance was there evidence of primary injury to the lower portion of the trachea, the bronchi or the lungs.

The aspiration of mucus or mucus and mucosal detritus from the upper portion of the trachea may result in the development of small and evanescent foci of pulmonary emphysema and atelectasis.

The explanation of the rapid warming of inhaled cold air and of the occurrence of relatively mild and localized injury following the inhalation of cold air lies in the fact that dry air has an extremely low heat capacity and that the number of calories required to produce a great rise in the temperature of dry air can be provided by the heat derived from the cooling of a small amount of tissue by a few degrees.

Although the intermittent exposure to cold air that occurs during normal respiration does not cause significant injury to the pharynx or larynx, a continuous exposure of these structures to cold may result in the development of a rapidly obstructive edema.

Experiments on dogs warrant the inference (a) that it is unlikely that significant injury to the air passages of man would result from the breathing of air at any degree of coldness likely to be encountered in nonexperimental conditions so long as it was inhaled through the nose or between partially closed lips and (b) that even though extremely cold air were inhaled rapidly through a widely opened mouth, it would be warmed to a point well above freezing by the time it reached the bronchi.

⁵ Smith, S. *Air Surgeon's Bull.* (no. 6) 1 17, 1944.

⁶ Milligan, C. B., Capt., M. A. C. Personal communication to the authors.

FATAL POISONING FROM POTASSIUM THIOCYANATE USED IN TREATMENT OF HYPERTENSION

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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During the last decade a revived interest in the treatment of arterial hypertension with thiocyanates, with varying degrees of success, has occurred. The toxic properties of these drugs have been known since the pharmacologic observations of Claude Bernard in 1857¹. Their noxious effects have been well recognized in recent years². The Council on Pharmacy and Chemistry of the American Medical Association has not accepted them and even has advised against their use³.

Great progress in the field was made by Barker in 1936^{2f} with the introduction of the practice of determining serially the blood content of thiocyanates. It was thought that with this method toxic blood levels, and therefore deleterious side effects, could be avoided. A few instances of serious and even fatal intoxication, however, have been recently reported. We have, unfortunately, had 1 such instance out of a series of 73 cases in which potassium thiocyanate was

used⁴. We feel that the report of cases like our own is necessary in order to speed the final and correct evaluation of this form of treatment.

The few cases hitherto published of death due to the therapeutic use of these drugs have presented a fairly uniform sequence of events⁵. Often a high degree of asthenia precedes the onset of symptoms. These are initiated with dysarthria and sometimes verbal aphasia and are followed by mental dulness, clonic contractures of the extremities and a deliriant state with visual or auditive hallucinations, sometimes with great mental and motor excitation. In fatal cases, despite the discontinuance of the drug with the onset of symptoms, there is a downhill course, with accentuation of the mental confusion, convulsions, stuporous state, coma, sphincter incontinence, collapse and death three to nineteen days from the beginning of symptoms.

REPORT OF CASE

A G, a white man aged 55, was admitted to the Hospital on May 17, 1943, complaining of dyspnea on exertion, tinnitus, photopsies and occurrence of palpitation during the preceding three months. He had also been suffering from muscular weakness, paresthesia in the right upper extremity and orthopnea during the month preceding admission. His past history was irrelevant except for an immoderate use of alcohol throughout most of his adult life and for a tendency to repeated nosebleeds for the past several years.

Physical examination disclosed a plethoric patient with a blood pressure of 230 systolic and 130 diastolic and with mild signs of congestive heart failure as indicated by the presence of dyspnea, slight cyanosis of the lips, tachycardia, pulmonary congestion, enlargement of the left side of the heart and some edema of the ankles. The liver was not remarkable, and ascites was not detected. A slight degree of dysarthria was present. The diagnoses of essential arterial hypertension, generalized arteriosclerosis of moderate degree and congestive heart failure were made.

4 del Solar, A, Dussailant, G, and Rodríguez, G. El tratamiento de la hipertensión arterial con el tiocianato de potasio, *Rev med de Chile* **72** 663-675 (Aug) 1944.

5 Russell, W O, and Stahl, W C. Fatal Poisoning from Potassium Thiocyanate Treatment of Hypertension, *J A M A* **119** 1177-1181 (Aug 8) 1942.

From the Clínica Médica del Hospital San Francisco de Borja, Escuela de Medicina de la Universidad de Chile (Prof A Garreton-Silva), Santiago, Chile.

1 Bernard, C. Leçons sur les effets des substances toxiques et médicamenteuses, Paris, J B Baillière et fils, 1857, p 354.

2 (a) Wald, M H, Lindberg, H A, and Barker, M H. The Toxic Manifestations of Thiocyanates, *J A M A* **112** 1120-1124 (March 25) 1939. (b) Goldring, W, and Chasis, H. Thiocyanate Therapy in Hypertension. Observations on Its Toxic Effects, *Arch Int Med* **49** 321-329 (Feb) 1932. (c) Garvin, C F. The Fatal Toxic Manifestations of the Thiocyanates, *J A M A* **112** 1125-1127 (March 25) 1939. (d) Lindberg, H A, Wald, M H, and Barker, M H. Observations on the Pathologic Effects of Thiocyanate, *Am Heart J* **21** 605-615 (May) 1941. (e) Healy, J C. Therapeutics and Toxicology of Sulfocyanates, *New England J Med* **205** 581-583 (Sept 17) 1931. (f) Barker, M H. Blood Cyanates in Treatment of Hypertension, *J A M A* **106** 762-767 (March 7) 1936.

3 Elixir Kacyan McNeil and Tablets Kacyan McNeil Not Acceptable for N N R, report of the Council on Pharmacy and Chemistry, *J A M A* **92** 1838 (June 1) 1929.

to 0.90 Gm he had begun to take about 1.34 Gm per day. Because of this and because of the clinical picture already described, the diagnosis of potassium thiocyanate intoxication was made. A high fluid intake and sedation with bromides were indicated. The following day the same abnormal signs somewhat more accentuated were observed, and, in addition, occasional deliriant episodes were noted. Cutaneous and tendinous reflexes were increased, and mild motor incoordination of the limbs, more pronounced in the right leg, was detected, the pulse rate was 96 per minute and the blood thiocyanate level 8.75 mg per hundred cubic centimeters.

In an attempt to increase the elimination of the drug and to minimize its deleterious effects on cellular respiration, the following therapeutic scheme was instituted: withdrawal of 600 cc of venous blood, continuous intramuscular injection of isotonic dextrose solution and administration of fluids by mouth freely, a total of 4 liters in the day being attained, 2 cc of esidrone (the sodium salt of pyridinedicarboxyl- β -mercuri- ω -hydroxypropylamide theophylline) intramuscularly, 75 mg of thiamine hydrochloride and 300 mg of nicotinamide in divided doses intravenously, 300 mg of ascorbic acid and 0.20 Gm of digitalis leaf (maintenance dose) by mouth were also administered.

During the following days this treatment was completed with the addition of aminophylline, metrazol and nikethamide as respiratory stimulants and administration of riboflavin (3 mg per day) parenterally and adequate amounts of fluid was continued. Few changes were observed in the condition of the patient until the fourth day of intoxication, when he fell into a comatose state with tachycardia and Cheyne-Stokes respiration, no additional changes were noted in the fundi. A spinal tap was performed and 10 cc of fluid of normal appearance was withdrawn, chemical examination disclosed a thiocyanate content of 10 mg per hundred cubic centimeters, 0.1 per cent albumin with 1 white blood cell per cubic millimeter and 0.64 per cent chlorides, the fluid was otherwise normal. Neurologic examination disclosed the presence of a slight spastic right hemiparesis, the neurologists' ⁷ opinion was that the patient had essentially the picture of a toxic encephalopathy and, in addition, slight signs of focal damage in the left hemisphere, and they suggested that these might correspond to an old lesion that had been made more prominent by the encephalic intoxication itself. They considered other possibilities, i.e., a meningocortical hemorrhage or other acute vascular accident, as remote. The same conditions were found and the same diagnosis was maintained on subsequent neurologic examinations.

On the fifth day of illness the patient recovered consciousness and blood pressure readings showed a decided drop, to 130 mm systolic and 90 mm diastolic. No additional changes were noted in the ocular fundi, a complete blood count exhibited normal values for hemoglobin and erythrocytes and a hyperleukocytosis (16,500 cells) with strong hyperregenerative deviation to the left. The next day aminophylline, analeptics, thiamine hydrochloride and riboflavin were discontinued and hypertonic dextrose solution intravenously was prescribed to overcome a state of anuria that had appeared in the morning of that day and that lasted twenty-four hours.

Except for the appearance of some pitting edema in the legs, no significant changes were noted on subsequent days. On August 5 the total cholesterol level, found to be 148 mg on admission, had fallen slightly,

to 130 mg per hundred cubic centimeters of blood. A similar fall of blood protein to slightly subnormal values was also noted, the value on August 11 was 5.44 Gm per hundred cubic centimeters, with an albumin-globulin ratio of 1.2. On August 10, the fourteenth day of illness, the patient again became deeply stuporous, physical examination showed signs of bronchopneumonia in the base of the right lung. Finally, on the sixteenth day, the patient's condition became critical. Blood pressure values of only 95 mm systolic and 50 mm diastolic, pronounced stertorous dyspnea and relaxation of sphincters supervened. He died in collapse in the morning of that day.

Necropsy ⁸—The significant observations were as follows:

Gross Examinations In the brain there was a small area, the size of a nut, of very recent hemorrhagic encephalomalacia in the left occipital lobe. In addition to this, two 3 by 1 by 1 cm areas of old and well



Fig 2—Section from a kidney. Hematoxylin and eosin stain, $\times 200$.

capsulated encephalomalacia were also found, one in the white matter close to the external aspect of the right lenticular nucleus and the other in the left hemisphere involving the external face of the optic thalamus and part of the anterior arm of the internal capsule. There existed decided arteriosclerosis at the base of the brain. The heart was moderately enlarged and hypertrophic, with a small patent foramen ovale, coronary arteriosclerosis and slight diffuse myocardial scarring of vascular type. In the aorta atheromatous plaques in moderate number were observed. The right kidney weighed 200 Gm, the left, 230 Gm. The surface was finely granular, with a small number of scars of vascular type, renal arteriosclerosis was observed. Confluent bronchopneumonia of the lower lobe of both lungs was found. Hyperplasia of the prostate with hypertrophic bladder muscle and an isolated gallbladder stone were observed.

⁷ Drs E. Uiberal and R. Nuñez B. assisted as consultant neurologists.

⁸ Prof. H. Rodríguez H. and Dr. C. Medina L. made the complete pathologic study in this case.

Microscopic Examinations Sections from both the damaged and the undamaged areas in the brain, heart muscle, liver, lungs, kidneys and bone marrow failed to disclose specific alterations ascribable to the drug. On the periphery of the right occipital lobe softening, inflammatory infiltration and neuroglial proliferation of slight degrees and few macrophages, some containing lipid droplets and hemosiderin inclusions, were found. Sections from the kidneys showed a diffuse and irregular inflammatory infiltration of mononuclear and polymorphonuclear cells with occasional involvement of the glomeruli, most of which, nevertheless, appeared normal. There were occasional hemorrhagic interstitial foci. Small and medium-sized arteries appeared thickened by a process of obliterating endarteritis that, in correspondence with some small atrophic foci, completely occluded the vessel. The more prominent changes, however, were found in the convoluted tubules, especially in the proximal ones, they consisted in a marked cloudy swelling and frequently even necrosis of their epithelial lining, with coagulated albuminous material, degenerated epithelial cells and erythrocytes in their lumen (fig 2). These changes presented varying degrees of intensity in different sections. Calcic casts, especially in the collecting tubules, were also found. Sections from the liver, bone marrow and other organs disclosed no significant changes.

Table 1 shows the amounts of thiocyanate contained in different tissues of our patient⁹ compared with the

old left temporal encephalomalacia was also found and that in 4 of the other 5 cases of fatal therapeutic poisoning as shown in table 2 as well as in the 4 cases of toxic encephalopathy in the series of Barker and associates¹¹ the patients were all elderly persons. If this assertion proves to be true, it will indicate a clearcut contraindication to the use of potassium thiocyanate for hypertension, since injury to the brain tissue of significant degree is a common and frequently unrecognizable feature in the natural history of this disease.

The problem concerning the third area of thrombotic softening in the right occipital lobe is simpler. This was a rather recent lesion, as evidenced by its macroscopic appearance and the slight inflammatory reaction and phagocytic activities on section, and consequently should be regarded as a terminal event, possibly precipitated by the great decline of blood pressure that occurred during the intoxication.

Some comment should be made regarding the necrotic nephrosis found in this case. No mention

TABLE 1—Amounts of Drug in the Tissues in 3 Cases of Fatal Potassium Thiocyanate Poisoning

Author	Potassium Thiocyanate, Mg per 100 Gm						
	Brain	Heart	Kidney	Liver	Lung	Muscle	Spleen
Goldring and Chasis, 1932	18.0	9.7	15.4	9.2	17.0		14.5
Russell and Stahl, 1942		1.2	5.4	10.1			
Del Solar and associates, 1944	22.1	28.6	25.5	26.3	22.0	16.5	

values obtained in the other 2 cases of fatal poisoning in which such study has been performed¹⁰. It can be seen that in our case there was a fairly uniform distribution of thiocyanate in the tissues and the values were distinctly higher than in the other 2 cases.

COMMENT

The presence of the encephalic lesions already described might cast some doubt on the true cause of death in this patient. It should be pointed out, however, that two of the foci of encephalomalacia corresponded to old cicatricial "cured" lesions, therefore death cannot be ascribed to them alone. On the other hand, it is quite possible that an already damaged brain, with impaired blood supply, may represent a predisposing factor either for the establishment of the intoxication or for the fatal outcome of the case. In this connection it is interesting to point out that in Russell and Stahl's case⁵ an area of

of damage to the renal parenchyma from potassium thiocyanate either in human subjects or in experimental animals has been encountered in a fairly comprehensive review of the literature.⁴ Thus our case would appear as the first in the literature in which it has been observed. Some reservations must be made, however, relative to the use of a mercurial diuretic (esidrone) in the treatment of our patient. The possibility of death from mercurial poisoning must be considered. Although we could not say with certainty that the renal lesions were not due to the diuretic employed, we must point out that the picture presented by the patient during life was not at all the usual one observed in cases of mercurial poisoning or of mercurial nephrosis and repeated urinalysis showed no increase in the few red blood cells and the traces of albumin that the patient had shown since his admission to the hospital. Moreover, the conclusion that death may have been produced by a single small dose

9 For this determination an alcoholic extraction from the tissue was performed and the thiocyanate level determined by Barker's method but employing standard solutions prepared with alcohol.

10 Goldring and Chasis^{2b}, Garvin^{2c}, Russell and Stahl⁵.

11 Barker, M. H., Lindberg, H. A., and Wald, M. H. Further Experiences with Thiocyanates, *J. A. M. A.* **117**: 1591-1594 (Nov. 8) 1941.

of esidrone¹² given intramuscularly appears unlikely in the light of present knowledge and according to the data recently compiled on the subject by DeGraff and Nadler¹³

We state, therefore, that the excessive intake of the drug, together with the characteristic course and clinical features of the case and the high content of drugs in the blood, in the spinal fluid and most especially in the tissues, leaves us no doubt about the diagnosis of fatal thiocyanate poisoning. A survey of the literature shows that our patient is the seventh whose death was due to this form of treatment (table 2)

accordance with present knowledge, that this was not a suitable case for use of the drug. In our own case a distinct error in dosage appears as responsible for the death of the patient. The remaining case, reported by Garvin, appears therefore as the only one in which treatment was irreproachable, although the advanced age of the patient could be offered as an objection. It has been said,¹⁴ and we agree with the statement, that potassium thiocyanate should not be administered to patients over 60 because of poor tolerance.

TABLE 2—*Reported Cases of Fatal Poisoning from Thiocyanate*

Case	Author	Sex and Age	Dose, Gm	Blood Thio cyanate, Mg per 100 Oc	Autopsy	Drug in Tissues, Mg per 100 Gm	Comment
1	Lesser, 1898 ⁵	M, 58	? massive		Yes	Strong traces	Suicidal intent
2	Kobert, 1906 ^{2c}	F,	0.3				Questionable, small dose, incomplete data
3	Vintilescu and Popesco, 1916 ^{2c}	M, 27	100 ?	Present	Yes	Present	Suicidal intent
4	Saleeby, 1930 ^{2a}		0.3 daily		Yes		Doubtful, coronary and mesenteric thrombosis
5	Healy, 1931 ^{2c}	F, 67	9 (total in 10 days)				Therapeutic use
6	Healy, 1931 ^{2c}	F, 63	0.96 to 0.64 daily				
7	Goldring and Chasis, 1932 ^{2b}	F, 40	9.7 in 15 days, 0.65 daily		Yes	9.2 to 18	Therapeutic use
8	Goldring and Chasis, 1932 ^{2b}	F, 56	14.5 in 18 days, 0.80 daily				Therapeutic use
9	Garvin, 1939 ^{2c}	F, 71	9 in 15 days 0.32 to 0.96 daily	13.6, 18.6	Yes		Therapeutic use
10	Russell and Stahl, 1942 ⁵	M, 52	5.6 in 14 days, 0.4 daily	15.2, 21.7	Yes	4.2 to 10.1	Therapeutic use
11	Del Solar, Dussallant, Brodsky and Rodriguez, 1944	M, 55	18 in 22 days, 0.5 to 1.34 daily	7, 29	Yes	16.5 to 28.6	Therapeutic use, patient ingested more than prescribed dose

Table 2 presents a summary of the fatal poisonings hitherto reported. It can be seen that the first 3 cases represent instances of suicide or possibly of suicidal intent. The fourth case cannot be considered as an unquestionable instance of thiocyanate poisoning, since the toxic manifestations were mainly cutaneous, the dosage was small, determinations of thiocyanate were not done and, finally, death resulted from coronary and mesenteric thrombosis. The remaining 7 cases, including ours, appear, on the other hand, as genuine instances of fatal poisoning. In 4 of these (cases 5, 6, 7 and 8) no determination of blood thiocyanate level was done during the treatment and the doses employed appear excessive. Of the remaining 3 instances, in the case reported by Russell and Stahl before treatment there was a significant nitrogen retention, poor renal function and probably also some degree of congestive heart failure. We feel, in

accordance with present knowledge, that this was not a suitable case for use of the drug. In our own case a distinct error in dosage appears as responsible for the death of the patient. The remaining case, reported by Garvin, appears therefore as the only one in which treatment was irreproachable, although the advanced age of the patient could be offered as an objection. It has been said,¹⁴ and we agree with the statement, that potassium thiocyanate should not be administered to patients over 60 because of poor tolerance.

14 Griffith, J. C., Lindauer, M. A., Roberts, E., and Rutherford, R. B. Studies of Criteria for Classification of Arterial Hypertension. VI. Treatment with Thiocyanate. *Am Heart J* 21:90-93 (Jan) 1941. Robinson, R. W., and O'Hare, J. P. Further Experiences with Potassium Sulfocyanate Therapy in Hypertension, *New England J Med* 221:964-969 (Dec 21) 1939.

15 Barker^{2f} Barker, Linberg and Wald¹¹

16 Page, I. H., and Corcoran, A. C. Hypertension, in Steele, J. M., and others. *Advances in Internal Medicine*, New York, Interscience Publishers, Inc., 1942, p. 83.

12 Two cubic centimeters of esidrone contain 0.086 Gm of mercury.

13 DeGraff, A. C., and Nadler, J. E. A Review on the Toxic Manifestations of Mercurial Diuretics in Man, *J A M A* 119:1006-1011 (July 25) 1942.

has indicated that even with so-called therapeutic or even lower concentrations, serious intoxications may occur. Of the 3 fatal cases in which blood concentrations were determined it can be seen that in Garvin's the toxic symptoms appeared when the blood thiocyanate level had reached only 13.6 mg per hundred cubic centimeters, that in Russell and Stahl's case it was between 15.2 and 21.7 mg, and, finally, that in our case, probably the most conspicuous of all, the blood level had reached only 7 mg per hundred cubic centimeters when the intoxication began. It should be pointed out that the "important" blood concentrations on which the clinician must depend and on which the correct evaluation of the cases should be based are those obtained before or at the very onset of symptoms of toxicity and not the values obtained afterward. Thus in the 3 cases the cyanate level rose rather sharply during the course of the poisoning, possibly because of a sudden release of the stored drug from the injured tissues, but, at least in Garvin's case, it never reached the levels at which "serious toxicity" occurs, according to the experience of Barker and associates.

We feel, therefore, that the prevalent concepts regarding toxicity and mode of administration of thiocyanate should be partly modified. We favor now, with Crockett and Moench,¹⁷ the use of smaller doses than those usually prescribed. Amounts of from 0.1 to 0.3 Gm per day, depending on body weight, at the beginning and slowly increased afterward, the blood thiocyanate being carefully watched at the third and seventh day and thereafter at gradually increased intervals of one to four weeks, would appear convenient in our opinion.

Caviness and co-workers¹⁸ advocated treatment with the lowest effective blood level of the drug possible; they rarely found it necessary to increase the level over 9 mg per hundred cubic centimeters. Other authors also¹⁹ have found good responses in a certain number of cases with blood concentrations as low as 3 to 6 mg per hundred cubic centimeters. It is possibly a fact that somewhat better responses are

obtained with higher levels, as those of 8 to 12 mg as advocated by Barker, Linberg and Wald,¹¹ and, moreover, that some patients may respond only at these concentrations. We feel, nevertheless, that thiocyanate therapy should be restricted to patients who react with a decline of blood pressure on levels of from 2 to 5 mg per hundred cubic centimeters, as, fortunately, the majority of patients in our experience have done, and that higher levels than these are potentially toxic and should not be attempted.

Special care should be given to the gradient of ascent of blood thiocyanates. Abrupt ascents were obtained in the 3 fatal cases in which determinations of blood level were done. Thus in Garvin's case the level rose to 3.8 mg during the first five days and to 10 mg on the eleventh day of treatment; in Russell and Stahl's case it rose to 4.2 mg on the second day and to 15.2 mg nine days later. In our case the level rose from 2.5 to 7 mg in as short a span as seven days. It may be inferred from this that a too sharp increase in the blood thiocyanate content, perhaps around or over 0.75 mg per day, possibly means either an excessive retention of the drug in the body or an excessive dose. In both instances the abrupt ascent observed may be the forerunner of much higher and potentially toxic blood levels if the dosage is not sharply reduced.

The presence of low blood thiocyanate before death in our patient, despite the high content of drug in the tissues at necropsy is in disagreement with observations made on human beings and on animals,²⁰ which tend to demonstrate that the blood concentration of thiocyanate closely follows the concentration in the tissues. We have found no explanation for this, possibly in our case it was due to good urinary excretion of the drug and to the great power of retention of the tissues intoxicated with it.

CONCLUSIONS

In its struggle against disease medicine has created a certain number of therapeutic procedures that under some conditions may defeat the purpose for which they are administered, causing death. Such is the case with arsenical compounds for syphilis, sulfonamide compounds, digitalis, mercurial diuretics and others. After a long period of clinical and experimental observations and in view of the rather small number of deaths as compared with the imposing number of lives providentially saved, medical practice has come to justify their general use.

We are aware that authors with considerable experience and authority are enthusiastic advocates of the potassium thiocyanate therapy for

17 Crockett, K. A., and Moench, L. G. Potassium Thiocyanate Treatment of Hypertension, *J. A. M. A.* **120** 982 (Nov 21) 1942.

18 Caviness, V. S., Umphlet, T. L., Peasley, E. D., Bell, T. A., and Satterfield, G. H. Potassium Sulfo-cyanate in Treatment of Hypertension, *North Carolina M. J.* **2** 283 (June) 1943, abstracted, *J. A. M. A.* **117** 1046 (Sept 20) 1941.

19 Blaney, L. F., Geiger, A. J., and Ernst, R. G. Potassium Thiocyanate in the Treatment of Hypertension, *Yale J. Biol. & Med.* **13** 493-507 (March) 1941. Flexner, M. Medical Treatment of Hypertension, *South M. J.* **34** 917-921 (Sept) 1941, cited by Page and Corcoran.¹⁶

hypertension, having never observed seriously untoward reactions. This merely shows that such reactions are fortunately rare, but by no means should it cause disregard for the accumulated data on thiocyanate toxicity that less fortunate workers have contributed. The empiric use of thiocyanates is at the present time undergoing the phase of study necessary for the correct appraisal of any drug. Up to the present time it is known only that this therapy is able to relieve two of the manifestations of hypertensive disease, namely the high blood pressure and the symptomatic complaints, but it is not known how this treatment modifies the course and the prognosis of the disease. Moreover, a comprehensive statistical study of the frequency with which severe intoxications occur is lacking. If these two points are not favorably answered by the future, this form of treatment should be abandoned. There would be no justification for the use of a substance that produces no real benefits

in the disease for which it is administered, that is potentially toxic and that may even cause death.

SUMMARY

Another case, the seventh thus far reported, of death due to the therapeutic use of potassium thiocyanate for hypertension is added to the literature. A distinct fault in dosage on the part of the patient was responsible for the intoxication; it emphasizes the danger of prescribing the drug in easily inaccurately measured forms, like the solution for drop administration used for this case.

The thiocyanate concentration of the blood at the onset of toxic symptoms was only 7 mg per hundred cubic centimeters. The concentrations of the drug in the tissue are the highest ones thus far reported in similar instances. A prominent feature of the postmortem examination was the finding of an acute necrotic nephrosis that had produced no symptoms or signs during life.

VENESECTION FOR THE PLETHORIC PATIENT

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It is traditional to consider the well built, strong, plethoric, overweight person as a candidate for apoplexy or heart disease. Because of the lack of recorded observations to support this clinical impression, a study of the erythrocyte counts and hemoglobin contents of a series of proved cases of coronary thrombosis was made. A study of 58 cases in which there was either autopsy evidence or a series of electrocardiographic tracings typical of coronary thrombosis has revealed that only 8 per cent of the patients had an erythrocyte count of less than 4,500,000

TABLE 1—Erythrocyte Counts for Thirty-Six Men with Coronary Thrombosis

Per Cent of Patients				
3	8	47	36	6
Red Blood Cells in Millions				
6.0+	6.0-5.5	5.5-5.0	5.0-4.5	4.5-
6.11	5.90	5.41	4.96	4.40
	5.85	5.41	4.93	4.42
	5.74	5.40	4.92	
		5.39	4.91	
		5.31	4.84	
		5.30	4.78	
		5.27	4.75	
		5.22	4.70	
Mean 5.09		5.20	4.70	
		5.16	4.60	
		5.15	4.53	
		5.13	4.50	
		5.10		
		5.09		
		5.08		
		5.05		
		5.03		

per cubic millimeter and that only 11 per cent had a hemoglobin content of less than 13.0 Gm. There were 36 men, with a mean erythrocyte count of 5,090,000 per cubic millimeter, and 22 women, with a mean erythrocyte count of 4,850,000 per cubic millimeter. Six per cent of the men and 13.5 per cent of the women had an erythrocyte count of less than 4,500,000 per cubic millimeter.

A relation between the erythrocyte count and clotting tendency having been suggested, a

clotting study on 15 persons was made. Eight plethoric patients with evidence of either coronary or cerebral thrombosis and 7 controls, including plethoric, normal and anemic persons, were studied. These included patients with polycythemia vera, obesity, leukemia, chronic glomerulonephritis and Hodgkin's disease, as well as normal controls.

Hemoglobin was studied by the Sahli method, prothrombin time, by Quick's method. For hematocrit determinations heparin was the anticoagulant. A simple test for sensitivity to heparin described by de Takats¹ was used in this study. Ten milligrams of purified heparin

TABLE 2—Erythrocyte Counts for Twenty-Two Women with Coronary Thrombosis

Per Cent of Patients				
0	9	65	13½	13½
Red Blood Cells in Millions				
6.0	6.0-5.5	5.5-5.0	5.0-4.5	4.5-
	5.97	5.40	4.93	4.30
	5.90	5.05	4.92	3.78
		4.90	4.90	3.44
		4.80		
		4.80		
		4.85		
		4.80		
Mean 4.85		4.74		
		4.71		
		4.71		
		4.70		
		4.69		
		4.65		
		4.64		

was injected intravenously. The coagulation time was determined before the injection and ten, twenty, thirty and forty minutes after the injection. A finger tip of each patient was punctured with a standard automatic lance. The first drop of blood was wiped off, the second was taken up in a chemically clean capillary tube 1.0 mm in diameter, which was held in the hand during the determination for thermostatic control. The tube was broken every thirty seconds, and the appearance of the first thread of fibrin was taken as the end point.

From the departments of Medicine, Northwestern University Medical School and St. Joseph Hospital.

1 de Takats, G. Surg., Gynec. & Obst. 77:32-36, 1943.

measured from the time the second drop of blood appeared. The curves thus obtained were classified as showing hyporeaction if the coagulation time beginning ten minutes after the injection was four and a half minutes or less and hyperreaction if the coagulation time was over seven and a half minutes.

The results are shown in chart 1. In this chart the prothrombin time in percentage of normal and the reaction time to heparin (ten minutes) represents the clotting activity. When these factors are plotted against the erythrocyte counts, arranged serially from low to high, a definite increase of the clotting activity is seen to occur as the erythrocyte count increases.

TABLE 3—Hemoglobin Values for Fifty-Eight Patients with Coronary Thrombosis

Per Cent of Patients				
36	3	30	20	11
Hemoglobin in Grams				
16 0	16 0-15 0	15 0-14 0	14 0 13 0	13 0
18 2	15 2	14 8	13 4	12 6
18 0	15 1	14 5	13 4	12 5
18 0		14 5	13 3	12 0
17 5		14 5	13 3	11 9
17 4		14 5	13 2	11 8
17 3		14 5	13 2	8 8
17 0		14 5	13 2	
17 0		14 5	13 2	
16 8		14 5	13 2	
16 4		14 4	13 2	
16 4		14 3	13 1	
16 2		14 1		
16 1		14 0		
16 0		14 0	Mean	14 5
16 0		14 0		
16 0		14 0		
16 0		14 0		
16 0				
16 0				
16 0				

This correlation, although not exact in the individual case, shows a definite trend in the group, more pronounced in the plethoric persons than in the normal and anemic controls. De Takats has previously demonstrated that the response to heparin in patients with thrombosis is reduced. In this series, there is a high incidence of hyporeaction in the plethoric person without clinical evidence of thrombosis, and the erythrocyte count is uniformly elevated or in the upper limits of normal. The presence of a high erythrocyte count, a flat heparin tolerance curve or a short prothrombin time cannot be considered in itself to be a factor capable of precipitating thrombosis, but the presence of all three in a group of persons with a known tendency to thrombosis appears to provide more sus-

ceptibility once thrombus formation has been initiated

A study was then made of 3 patients with flat heparin tolerance curves to determine the effect of bleeding on the clotting mechanism. It was formerly believed that venesection provoked erythropoietic stimulation. However, it has been shown by Falconer,² Stephens and Kaltreider,³ Holbrook,⁴ Hines and Darnall⁵ and others that

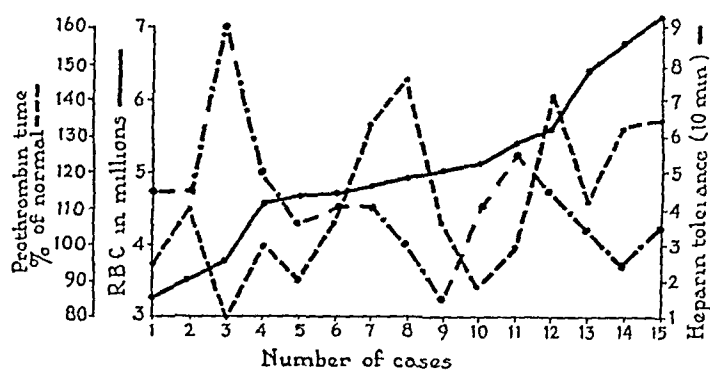


Chart 1—Fifteen cases The erythrocyte count is plotted serially from low to high The clotting index is plotted from the prothrombin time (in percentage of normal) and the reaction to heparin taken ten minutes after its injection

small (100 to 500 cc) frequent bleedings in patients with polycythemia vera controlled the symptoms and lowered the erythrocyte, hemoglobin and hematocrit values without producing a significant rise in the reticulocyte count. Three patients were studied: a normal control, a patient with polycythemia vera and a patient with

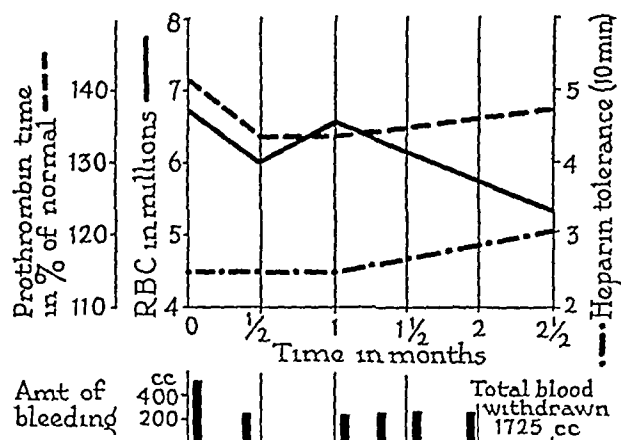


Chart 2—Results of bleedings in a patient with polycythemia vera

a recent coronary thrombosis. The patient with polycythemia vera was studied before, during and after a series of small bleedings. A total

- 2 Falconer, E H Ann Int Med 7 172-189, 1933
3 Stephens, D J, and Kaltreider, N L Ann Int
Med 10 1565-1581, 1937
4 Holbrook, A A Wisconsin M J 40 899-910,
1941
5 Hines, L E, and Darnall, W C Am J M
Sc 206 434-438, 1943

of 1,725 cc of blood was withdrawn in six bleedings over a period of two months. During this period the erythrocyte count decreased from 6,600,000 to 5,290,000 cells per cubic millimeter, the prothrombin time was slightly increased, and the response to heparin was slightly increased. From another plethoric patient with recent coronary thrombosis, auricular fibrillation and obesity, 800 cc of blood was withdrawn

produced a lessening of the clotting tendency, as evidenced by an increase in the prothrombin time and an elevation in the heparin tolerance. The same results were obtained in the patient with polycythemia vera, in which the tendency to thrombosis is well known. In contrast, the normal control showed no change in the prothrombin time, although the response to heparin was greatly diminished.

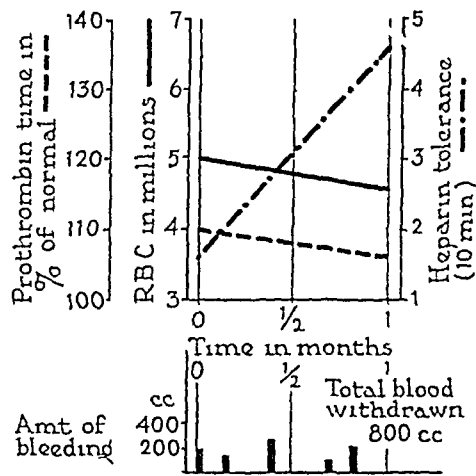


Chart 3—Results of bleedings in a patient with a recent coronary thrombosis

in five bleedings in one and a half months. The erythrocyte count dropped from 5,000,000 to 4,500,000 cells per cubic millimeter, the prothrombin time was slightly increased, and the response to heparin was noticeably increased. From a normal patient 1,350 cc of blood was withdrawn in four bleedings during a six week period. The erythrocyte count dropped from 5,400,000 to 4,290,000 cells per cubic millimeter, the prothrombin time was slightly shortened, and the response to heparin was reduced.

These studies show that small frequent bleedings in 1 patient (recent coronary thrombosis)

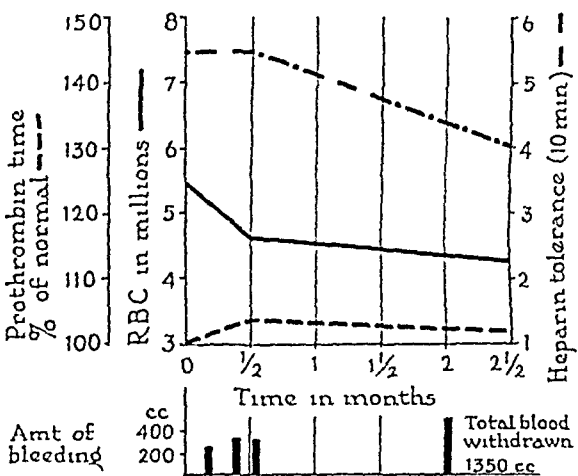


Chart 4—Results of bleedings in a normal person

SUMMARY

Only 2 of 58 patients proved to have had coronary thrombosis had an erythrocyte count of less than 4,000,000. Diminished clotting time after administration of heparin and a shortened prothrombin time were the common findings for patients with high erythrocyte counts.

Similar changes in the clotting mechanism have been observed in patients known to have thrombosis. These facts suggest that the use of venesection both for preventing and for treating thrombosis is rational. The changes produced by bleeding a small number of patients seem to support the idea.

Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM JULY 1943 TO JUNE 1944

WALTER LINCOLN PALMER, M D , DAVID S HARMAN, M D

AND

WILLIAM E RICKETTS, M D

CHICAGO

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INTRODUCTION

The publications dealing with gastroenterologic subjects reveal continued progress through the year, with no startling developments. The new chemotherapeutic agents, the sulfonamide compounds and penicillin, have proved perhaps least helpful in infections of the digestive tract.

Several excellent books have appeared, none of which can be reviewed in detail. Two of the three volumes of "Gastroenterology," written by Bockus,¹ have been printed and can be highly recommended. The second edition of "Diseases of the Digestive System," edited by Portis² is likewise excellent. Babkin³ has published an exhaustive treatise on the digestive glands. Rehfuess⁴ has written a commendable book on "Indigestion, Its Diagnosis and Management, with Special Reference to Diet." Templeton's⁵ "X-Ray Examination of the Stomach" is a splendid monograph on the roentgenologic examination of the upper part of the digestive tract. Hodges'⁶ book presents an up-to-date and practical consideration of roentgenologic gastroenterology. Dack's⁷ monograph on "Food Poisoning" is a classic. The second edition of Manson-Bahr's⁸ "Dysenteric Disorders" is an excellent reference text, as is the third edition of "Clinical Parasitology" by Craig and Faust.⁹ Borgen,¹⁰ chiefly on the basis of his own enormous experience with nonspecific ulcerative colitis, has written a splendid monograph on the "Modern Management of Colitis." Several review articles have appeared, such as those on

roentgenology by Rigos and Kirklin,¹¹ on diseases of the colon by Wollaeger and Borgen¹² and on tropical disease by Faust,¹³ as well as Faust's¹⁴ review of amebiasis in his Alvarenga Prize Lecture. Bethell and associates¹⁵ have reviewed the literature dealing with the relationship between gastritis, pernicious anemia and gastric neoplasm, and Reimann¹⁶ has reviewed that pertaining to intestinal infections.

ESOPHAGUS

Motility—McLaren¹⁷ studied kymographically the movement of food down the esophagus and found that a wave of contraction moves at an average speed of 3 inches (7.5 cm) in two seconds. The wave, increasing in length as it progresses, appears to push the food along without a preceding wave of relaxation.

Esophageal Pain—Moersch and Miller,¹⁸ in an excellent review of esophageal pain, comment on the scarcity of knowledge concerning the innervation of the esophagus and the uncertainty regarding the pathway for the conduction of pain. Experimentally and clinically, the mechanism of pain seems to consist chiefly in stretching of the esophagus with resultant increase in the tension. The pain is much more likely to occur with acute ulceration, inflammation and presumably associated spasm than with slow-growing lesions, such as carcinoma. There are wide variations among individuals as regards susceptibility to and the radiation of esophageal pain. The great difficulty in distinguishing at times between angina pectoris and the pain of hiatus hernia is emphasized.

1 Bockus, H. L. *Gastroenterology*, Philadelphia, W. B. Saunders Company, 1943, vol. 1, 1944, vol. 2.

2 Portis, S. A. *Diseases of the Digestive System*, ed. 2, Philadelphia, Lea & Febiger, 1944.

3 Babkin, B. P. *Secretory Mechanism of the Digestive Glands*, New York, Paul B. Hoeber, Inc., 1944.

4 Rehfuess, M. E. *Indigestion: Its Diagnosis and Management*, Philadelphia, W. B. Saunders Company, 1943.

5 Templeton, F. E. *X-Ray Examination of the Stomach*, Chicago, University of Chicago Press, 1944.

6 Hodges, F. *The Gastro-Intestinal Tract: A Handbook of Roentgen Diagnosis*, Chicago, The Year Book Publishers, Inc., 1944.

7 Dack, G. M. *Food Poisoning*, Chicago, University of Chicago Press, 1943.

8 Manson-Bahr, P. *The Dysenteric Disorders*, ed. 2, Baltimore, Williams & Wilkins Company, 1943.

9 Craig, C. F., and Faust, E. C. *Clinical Parasitology*, ed. 3, Philadelphia, Lea & Febiger, 1943.

10 Borgen, J. A. *The Modern Management of Colitis*, Springfield, Ill., Charles C. Thomas, Publisher, 1943.

11 Rigos, F., and Kirklin, B. R. *Diagnostic Roentgenology in Gastroenterology for the Year 1941*, *Gastroenterology* **1**: 669-686 and 942-960, 1943.

12 Wollaeger, E. E., and Borgen, J. A. *The Large Intestine: A Review of Current Literature*, *Gastroenterology* **2**: 102-120, 1944.

13 Faust, E. C. *Diseases in Tropical Zones*, *Gastroenterology* **1**: 995-1012, 1943.

14 Faust, E. C. *Some Modern Conceptions of Amebiasis*, *Science* **99**: 45-51 and 69-72, 1944.

15 Bethell, F. H., Sturgis, C. C., Mallery, O. T., Jr., and Rundles, R. W. *Blood: A Review of the Recent Literature*, *Arch. Int. Med.* **74**: 37-39 (July) 1944.

16 Reimann, H. A. *Infectious Diseases: Tenth Annual Review of Significant Publications*, *Arch. Int. Med.* **74**: 287-291 (Oct.) 1944.

17 McLaren, J. W. *Kymography and Its Application to Esophageal Movement*, *Brit. J. Radiol.* **16**: 270-273, 1943.

18 Moersch, H. J., and Miller, J. R. *Esophageal Pain*, *Gastroenterology* **1**: 821-831, 1943.

Atresia—Singleton and Knight¹⁹ report 4 cases of congenital atresia of the esophagus with tracheoesophageal fistulas. Three of the patients died, 1 after gastrostomy, 1 after a posterior extrapleural operation in which the fistula was ligated and the third after a transpleural operation in which the fistula was ligated and an esophageal anastomosis made. In the fourth case a gastrostomy was done, after which through a transpleural approach the fistula was ligated with an end to end anastomosis of the esophagus.

The child lived seven months. The advantages of the transpleural approach are enumerated. Ladd²⁰ discussed the different types of tracheoesophageal fistulas and esophageal atresia. Since 1939, 34 patients have been operated on with his method, 6 with primary anastomosis of the esophagus, 2 surviving; 28 had the three stage operation consisting of obliteration of the esophageal fistula, gastrostomy and esophagostomy, 9 surviving. The primary anastomosis of the esophagus is considered the procedure of choice when the ends of the esophagus can be approximated. Humphreys²¹ reviews the 134 cases published in the literature and includes 19 of his own in which operation was performed for congenital atresia of the esophagus. Twenty-four babies have survived operation and are still living today. A direct anastomosis was successful in 8, in 16 the fistula was divided in the mediastinum, the upper segment being brought out in the neck and a gastrostomy made for feeding purposes. Royer²² reports the case of a 7 year old boy with a congenital stenosis of the esophagus of the canalicular type treated successfully by means of progressive dilation of the esophagus.

Esophagitis—Brown²³ placed a group of 17 white rats between 2 and 3 months of age on a diet of Texas rice with cottonseed oil in the ratio of 20 cc of oil and 1,000 Gm of rice and a slice of fresh carrot for a period of six months. No consistent abnormality was noted in any organs other than the esophagus. Seven rats had ulcers

in the lower part of the esophagus and 1 an ulcer of the forestomach. Hyperkeratosis and various stages of inflammation, muscular atrophy and fibrosis were noted. Such lesions were rarely found in a control group.

Paul²⁴ describes 5 cases of esophagitis resulting in stricture formation. In 1 it followed the use of a negative pressure tube for a week and was relieved by numerous esophageal dilation. In 1 case it was associated with a congenitally short esophagus with an esophageal hiatus hernia. In 1 case there was an esophageal stricture associated with a ruptured peptic ulcer. In another case the stricture was associated with an ulcer of the lesser curvature of the stomach. In the fifth case it developed over a period of three years and was accompanied with diffuse intermittent spasm of the lower half of the esophagus. Paul emphasizes the probable role of acid gastric juice in the production of the esophageal ulceration. The roentgenologic changes consist of the severe spasm of the distal part of the esophagus, loss of mucosal folds and a fine roughening of the surfaces. If the lesion is present for a sufficient length of time, the roentgen findings may be those of a diffuse fibrous stricture. In some cases of chronic esophagitis the most striking roentgenologic manifestation is intermittent diffuse spasm of the lower half or third with thickening of the mucosal folds. The appearance is much different from "curling of the esophagus."

Ulcer—Cleaver,²⁵ in a well documented and well illustrated presentation of 10 cases of peptic ulceration of the esophagus, describes the definite clinical and radiologic manifestations and the quite constant association with a congenital short esophagus or a diaphragmatic hernia, permitting regurgitation of acid contents from the stomach into the esophagus. Similarly, ectopic gastric mucosa in the esophagus can produce chronic ulceration, as shown by biopsy in 2 cases and in a third reported by Bonorino Udaondo, d'Alotto and Nasio²⁶. Peptic ulceration was associated with a short esophagus in all the cases observed by Johnstone²⁷. Congenital shortening might account for ulceration in children. However, the frequent occurrence in old age is ascribed to loss of elasticity of tissue in the aged, with re-

19 Singleton, A. O., and Knight, M. D. Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula, *Ann Surg* **119** 556-572, 1944.

20 Ladd, W. E. The Surgical Treatment of Esophageal Atresia and Tracheoesophageal Fistulas, *New England J Med* **230** 625-637, 1944.

21 Humphreys, G. H. The Surgical Treatment of Congenital Atresia of the Esophagus, *Surgery* **15** 801-823, 1944.

22 Royer, M. Estenosis congenita canalicular del esofago, curacion con la dilatacion, *Arch argent de enferm d ap digest y de la nutrición* **18** 697-703, 1943.

23 Brown, C. E. Dietary Ulcers of the Esophagus of the Rat, *Am J Path* **19** 785-796, 1943.

24 Paul, L. W. Roentgenologic Aspects of Acute and Chronic Esophagitis, *Radiology* **41** 421-430, 1943.

25 Cleaver, E. E. Chronic Peptic Ulceration of the Esophagus, *Am J Digest Dis* **10** 319-329, 1943.

26 Bonorino Udaondo, C., d'Alotto, V., and Nasio, J. Ulcera peptica del esófago, *Prensa méd argent* **29** 1342-1347, 1943.

27 Johnstone, A. S. Peptic Ulceration of the Esophagus with Partial Thoracic Stomach, *Brit Radiol* **16** 357-361, 1943.

sultant shortening of the esophagus and laxity of the hiatus. Increased abdominal pressure may cause a small portion of the stomach to slip freely through the hiatus, forming a reducible thoracic portion of the stomach. The laxity of the hiatus permits regurgitation of gastric juice. The diagnosis of peptic ulceration and partial thoracic stomach is essentially roentgenologic, the important feature being the demonstration of both esophageal and gastric mucosa above the diaphragm. With ulceration there may be narrowing due to spasm at the junction of esophagus and stomach.

Mediastinitis—Hawes²⁸ reports that roentgenologic examination of the barium-filled esophagus is a definite aid in the differentiation of mediastinal infection and tumor. As observed in 5 cases of active mediastinal tuberculosis, the appearance of the esophagus is changed by pressure, by adhesions and by actual involvement of the mucosal surface. The presence of adhesions is indicated in the roentgenogram by a number of projections, appearing either as points or rounded waves, in the involved segment of the esophagus. These projections are constant and probably are produced by traction.

Mascheroni, Reussi and Lafage²⁹ describe a 49 year old man with spasm of the lower part of the esophagus in whom after esophagoscopy a transitory esophagomediastinal fistula and abscess of the lung developed. Recovery occurred gradually with the administration of 0.5 Gm of sulfathiazole every three hours for twenty-eight days. Grace and Irwin³⁰ report perforation of the cervical portion of the esophagus by a plastic denture resulting in mediastinitis, treated by surgical drainage, with recovery and no evidence of esophageal obstruction.

Scleroderma—Hale and Schatzki³¹ studied 22 patients with scleroderma. In 5 of 7 patients complaining of dysphagia the esophagus was abnormal, similar abnormalities were also found in 8 patients without symptoms. The abnormalities consisted mainly in delayed emptying combined with a decrease in peristalsis in the lower half of the esophagus. There was no

gross dilatation as in cardiospasm. Barium sulfate passed into the stomach in a slow but constant trickle. There was a tendency for the esophagus to remain open after the main bolus had passed, to contain a large amount of air and to be outlined by barium abnormally adherent to the wall.

Varices—Welt and Blatteis³² report massive hemorrhage from esophageal varices attributed to portal obstruction resulting from scar tissue formation following multiple hepatic abscesses secondary to appendical peritonitis. The patient was treated successfully during a period of bleeding by injection of the sclerosing solution into the esophageal veins. Duffy and Fraser³³ report another instance of fatal bleeding from esophageal varicosities with splenomegaly of unknown cause and a normal liver at autopsy.

Cardiospasm—Weiss³⁴ considers cardiospasm as an organ neurosis, a form of conversion hysteria deeply rooted in the unconscious mental life of the individual. It arises coincident with an emotional conflict in a person whose early life gives evidence of personality difficulties. Exacerbations frequently can be correlated with fresh psychic insults touching the particular complex of the individual. Psychosomatic observations in 9 cases are reported.

Roentgenologically the elongated tortuous and kinked esophagus may be seen to encroach on the pulmonary fields, but it is easily distinguished roentgenologically even though there is seldom a fluid level³⁵. The shadow is relatively opaque and may be mistaken for other types of mediastinal enlargements. D'Silva³⁶ describes a dilated esophagus discovered on routine examination of the chest and differing from the usual cases by the absence of symptoms and of evident spasm and by the abnormal shape and length of the esophagus. Hurst³⁷ reports on 9 patients with respiratory symptoms resulting from pressure of the distended esophagus or from aspiration of regurgitated food. In 1 patient the condition was mistaken for a mediastinal tumor, in 1 pleural effusion developed secondary to aspira-

32 Welt, B, and Blatteis, S. R. Esophageal Varices. Case Report, *Am J Surg* **63** 415-417, 1944.

33 Duffy, D. G., and Fraser, A. N. Fatal Bleeding from Esophageal Variococities, *M J Australia* **1** 202-204, 1944.

34 Weiss, E. Cardiospasm. A Psychosomatic Disorder, *Psychosom Med* **6** 58-70, 1944.

35 Williams, E. R. Dilatation of the Esophagus, *Brit J Radiol* **16** 220, 1943.

36 D'Silva, J. L. Symptomless Enlargement of the Oesophagus, *Brit M J* **1** 750-751, 1944.

37 Hurst, A. Respiratory Complications of Achalasia of the Cardia with Mega-Oesophagus, *Guy's Hosp Rep* **92** 68-73, 1943.

28 Hawes, L. E. The Roentgenological Changes in the Esophagus in Tuberculous Mediastinitis, *Am J Roentgenol* **5** 575-584, 1944.

29 Mascheroni, H. A., Reussi, C., and Lafage, L. A. Fistula esofagomediastinica post-esofagoscopia, absceso de pulmon, curacion, *Arch argent de enferm d ap digest y de la nutricion* **18** 712-722, 1943.

30 Grace, K. D., and Irwin, T. M. Perforation of the Cervical Esophagus with Mediastinitis, *Surgery* **14** 631-639, 1943.

31 Hale, C. H., and Schatzki, R. The Roentgenological Appearance of the Gastro-Intestinal Tract in Scleroderma, *Am J Roentgenol* **51** 407-420, 1944.

tion pneumonia, and 2 had paroxysmal coughing from regurgitation of food. In the case of the tenth sudden death resulted from asphyxia produced by obstruction of the glottis with regurgitated food.

Vines and Olsen³⁸ describe a 50 year old man with cardiospasm who had the typical picture of pellagra and was cured by nicotinic acid amide. The rarity of deficiency disease in patients with esophageal lesions is attributed to the fact that it seems less likely to develop in persons with partial starvation than among persons with poorly balanced diets.

Bersack,³⁹ in 227 patients with esophageal carcinoma, found 1 with associated achalasia of the cardia. Since dilatation of the cardia may delay the appearance of obstructive symptoms, frequent esophagoscopies are recommended for such patients. Bonorino Pero and Coppola⁴⁰ report the well documented and illustrated case of a 38 year old woman with megaesophagus for twenty-three years in whom a carcinoma of the middle of the esophagus finally developed.

Lichstein⁴¹ describes a 50 year old white woman with an enormous tortuous esophagus due to cardiospasm for whom medical treatment over a period of three years availed little. Esophagogastrostomy was performed successfully with almost complete symptomatic relief in spite of the fact that the new stoma did not seem to function well, as seen roentgenologically. This discrepancy between symptomatic relief and the behavior of the new cardia evident by roentgenologic examination has been noted by others following surgical treatment of this type and, indeed, is well known to exist after medical treatment, i.e., mechanical dilation of the cardia. Esophagogastrostomy is considered the treatment of choice for patients with cardiospasm not responding satisfactorily to dilatation.

Carcinoma—Fleming,⁴² in studying 42 cases of carcinoma of the esophagus, found that when the linear involvement exceeded 5 cm there was

a material increase in the metastases, suggesting a rough relationship between the size of the lesion and the extent of the spread. There was a high incidence of metastases to the liver. Since the majority of these lesions are squamous cell epitheliomas and such tumors elsewhere respond to irradiation therapy, Fleming suggests that such therapy might be more effective if a wider and shorter field of radiation were used rather than the usual long, narrow field. Smithers,⁴³ on the other hand, prefers the long narrow fields using six portals, one anterior, one posterior and four oblique. Although there have been no startling results, the relief of symptoms has been very much worth while and palliation can be obtained in many cases.

The most significant progress in esophageal disease has been made in recent years in the surgical treatment of carcinoma, intractable cardiospasm and stricture. Reports of successful transthoracic operations with or without resection of portions of the esophagus and, if indicated, of the stomach also have now come from many countries.⁴⁴

STOMACH

Anorexia Nervosa—Oppenheimer⁴⁵ illustrates the resemblance in the clinical picture of Simmonds' disease to anorexia nervosa, low basal metabolic rate, low blood sugar level, long duration of the symptoms, no relief from psychotherapy and yet at autopsy no abnormalities of the pituitary. Oppenheimer considers this an instance of "pseudo Simmonds' disease," 14 similar cases being reported in the literature.

43 Smithers, W. D. The X-Ray Treatment of Carcinoma of the Esophagus, *Brit J Radiol* **16** 317-322, 1943.

44 (a) Ferrari, R. C. El tratamiento quirúrgico de las enfermedades del esófago, *Arch argent de enferm d ap digest y de la nutrición* **18** 651-696, 1943. (b) Clagett, O. T., and Wigg, L. M. Trans-thoracic Resection of Esophagus and Stomach for Carcinoma. Report of Two Cases, *Proc Staff Meet, Mayo Clin* **18** 337-344, 1943. (c) Steele, G. H. Carcinoma of the Oesophagus, *Lancet* **2** 797-798, 1943. (d) Resano, J. H. Cancer del esófago resección y anastomosis (los éxitos operatorios), *Arch argent de enferm d ap digest y de la nutrición* **19** 119-134, 1944. (e) Yurasov, E. E. Reconstruction of Esophagus, *Am Rev Soviet Med* **1** 206, 1944. (f) Brea, M. M. Tratamiento quirúrgico del cancer del esófago torácico, *Medicina, Buenos Aires* **4** 74-86, 1943. (g) Señorans, A. J. Consideraciones sobre patología del esófago, *Arch argent de enferm d ap digest y de la nutrición* **18** 557-579, 1943. (h) Gotta, G. Radiología del esófago, *ibid* **18** 580-607, 1943. (i) Brachetto-Brian, D. Patología del esófago, *ibid* **18** 608-650, 1943.

45 Footnote omitted.

46 Oppenheimer, B. S. Simmonds' Disease Versus Anorexia Nervosa. A Report of a Case with Necropsy Findings, *J Mt Sinai Hosp* **10** 640-650, 1944.

38 Vines, R. W., and Olsen, A. M. Cardiospasm with Associated Pellagra. Report of Case, *Proc Staff Meet, Mayo Clin* **18** 389-395, 1943.

39 Bersack, S. R. Carcinoma of the Esophagus in Association with Achalasia of the Cardia, *Radiology* **42** 220-223, 1944.

40 Bonorino Pero, C., and Coppola, J. A. El cancer como complicación del megaesófago, *Prensa med argent* **30** 2136-2140, 1943.

41 Lichstein, J. Cardiospasm. Successful Treatment by Esophagogastrostomy, *Am J Digest Dis* **10** 271-275, 1943.

42 Fleming, J. A. C. Carcinoma of the Thoracic Esophagus. Some Notes on Its Pathology and Spread in Relation to Treatment, *Brit J Radiol* **16** 212-216, 1943.

Pernicious Vomiting of Pregnancy—For thirty years Sir Arthur Hurst⁴⁷ has been convinced that the so-called pernicious vomiting of pregnancy is always hysterical. Fifty or 60 deaths from it are registered in England annually. Most modern textbooks discuss the differentiation between the toxic and the nervous form of pernicious vomiting of pregnancy. Gibberd teaches that in the rare cases in which Korsakoff's syndrome of peripheral neuritis with mental symptoms develops the vomiting is toxic in origin because of the resemblance of the clinical and pathologic conditions to those produced by alcohol. Hurst contends that these are rarely the results of the associated vitamin D deficiency and that there is no qualitative difference between the two types. A woman of 32 with continued vomiting, a pulse rate of 136 and pronounced emaciation was told by her father that she would have a bad time in pregnancy, as her mother had vomited all the time that she was pregnant. Hurst explained to her that there was no good reason why she must vomit after the first six weeks, in which vomiting is normal, and that her father's suggestion was all that was needed to lead to her present condition. In ten minutes he convinced her that she would not vomit again. Later he returned and watched her eat buttered toast and tea, which she had chosen for her first meal. There was no inclination to vomit then or at the following supper, but she did vomit the next morning. She was then transferred to a better psychologic environment and had no further trouble. Eleven months after delivery she again became pregnant and at once began to vomit so severely that her physician discussed termination of the pregnancy. The vomiting again yielded to psychologic treatment. Hurst thinks that toxemic vomiting of pregnancy, apart from that associated with eclampsia or acute hepatic necrosis, does not occur. Jaundice, however, may result from hysterical vomiting and disappears rapidly with an adequate diet.

Diaphragmatic Hernia—Bremer⁴⁸ studied the embryonic development of the diaphragm and the different types of diaphragmatic hernia. Murphy and Hay,⁴⁹ in an excellent study of 72 patients with hiatus hernia, found anemia of

different degrees, usually of the hypochromic type, in 70 per cent.

Symptoms, according to Turner,⁵⁰ may be absent or they may be varied, but they consist typically in anginoid pain, worse after meals, aggravated by the horizontal position and frequently accentuated by emotional stress. Distention of the lower third of the esophagus has been shown to produce anginoid pain, pyrosis and heartburn. In the roentgenologic demonstration of hernia, the Muller maneuver is of value. Interference with the vascular supply of the herniated stomach may cause congestion of the mucosa, gastritis and even peptic ulceration. The formation of fibrous adhesions to the left dome of the diaphragm may cause pronounced local circulatory embarrassment and even pain in the left shoulder. Hiatus herniation was found on 35 per cent of 1,500 examinations of the upper part of the gastrointestinal tract. Hernias are more easily visualized in a slight Trendelenburg position. The demonstration of gastric rugae traversing the hiatus suffices for a positive diagnosis. Persistently prominent rugal folds suggest vascular interference in the hernia. A broadly dilated esophageal hiatus with a mobile and distensible herniated portion of the stomach and a normal rugal pattern is least often connected with symptoms. Conversely, a portion of stomach persistently herniated at the hiatus with no mobility, limited distensibility and decided prominence of rugal pattern is most likely directly productive of symptoms.

Of the many complications coincidental to hiatus hernia, total volvulus of the stomach is one of the rarest and most serious. A left diaphragmatic hernia was reported⁵¹ with attacks of pressure, apparently induced as a result of conscious or subconscious emotional reactions and relieved by spontaneous or induced belching or vomiting. Volvulus of the distal half of the stomach finally resulted, with rotation anteriorly and upwards. The subsequent incarceration of the antrum in the left hernial sac with complete kinking of the antrum produced total acute gastric obstruction. A method of obliterating the hernial sac by tamponade was employed with apparently good results.

Gastric Motility—Van Liere and Northup⁵² found that the addition of 500 cc of tap water

47 Hurst, A, cited, *Hysterical Nature of the So-Called Pernicious Vomiting of Pregnancy*, *Foreign Letters* (London), J A M A **125** 223 (May 20) 1944.

48 Bremer, J L. *The Diaphragm and Diaphragmatic Hernia*, *Arch Path* **36** 539-549 (Dec) 1943.

49 Murphy, W P, and Hay, W E. *Symptoms and Incidence of Anemia in Hernia at the Esophageal Hiatus*, *Arch Int Med* **72** 58-68 (July) 1943.

50 Turner, J W. *Gastric Herniation at the Esophageal Hiatus*, *Am J Roentgenol* **50** 33-41, 1943.

51 Vorhaus, M G, and Stetten, DeW. *Volvulus and Incarceration of Stomach in a Diaphragmatic Hernia with Complete Acute Gastric Obstruction*, *Gastroenterology* **2** 307-315, 1944.

52 Van Liere, E J, and Northup, D W. *The Effect of Water Taken with Meals on Gastric Emptying*, *Gastroenterology* **2** 195-200, 1944.

to a standard 200 cc test meal exerted no appreciable effect on the gastric emptying time nor did the addition of 1,000 cc of water except in 1 instance

Significant prolongation in gastric emptying time was observed by Jacobson and Palmer⁵³ in patients whose peripheral erythrocyte count was below 1,500,000. Contrary to the general belief that gastrointestinal motility is increased and the passage of material from the stomach and through the intestinal tract accelerated in pernicious anemia, these functions were found to be normal or delayed. Achlorhydria per se does not significantly affect the rate of gastric emptying.

A study made by Henschel, Taylor and Keys⁵⁴ of the decreased appetite frequently observed in hot weather disclosed that the emptying time is actually faster at the higher temperatures. Twelve of the subjects had an average decrease of 30 per cent. Observations on about 100 normal men doing hard work at 120° F failed to indicate any lack of appetite or any signs of decreased gastric activity except in actual heat exhaustion.

Extracts of the urine of patients with duodenal ulcer and of normal human males administered intravenously inhibit the gastric motility of dogs with gastric fistula, the amount required being three to five times that needed to depress gastric secretion⁵⁵. The motility-inhibiting factor appears to be distinct from the ulcer prevention and healing factor.

Hoelzel⁵⁶ subjected himself to a thirty-three and a forty-one day fast in order to study the effect on gastric activity of starvation and realimentation with various types of foodstuffs. The results are interpreted as being in accord with the author's previous observations on the importance of proteins. The role of subjective factors in such work is difficult for us, the reviewers, to appraise.

Twenty-five experiments measuring changes in gastric motor activity occurring before and

during nausea produced by a variety of stimuli were carried out by Wolf⁵⁷ on 4 human subjects. The earliest change noted was a cessation of gastric contraction with a decrease in tone. Prolonged or increased stimulation would result in nausea, sweating, pallor of the face and gastric mucosa and tachycardia. When neostigmine hydrobromide, 0.015 Gm, and atropine sulfate, 0.012 Gm, were given, vigorous gastric contractions were produced that persisted in spite of stimuli that produced vertigo and nystagmus and had previously produced cessation of gastric motility. Nausea did not occur. No predictable effect was produced when neostigmine or atropine was given alone. Nausea occurred only during phases of inhibited gastric motility.

Airsickness, seasickness, trainsickness and sickness produced by amusement parks are all characterized by symptoms related to the gastrointestinal tract. Motion sickness was produced experimentally in 100 subjects undergoing testing for a twenty minute period⁵⁸. Fluoroscopic studies were made of the gastric tone, the gastric peristalsis, the correlation between peristalsis and gastric tone, pylorospasm, intestinal progress and intestinal pattern. Two groups were separated: 28 per cent that became sick and 72 per cent that were immune. No specific type of gastrointestinal tract from either an anatomic or a functional standpoint was associated with susceptibility to motion sickness. A definite decrease in gastric tone and in peristalsis occurred after the motion test in a significant number of subjects. Changes in gastric tone and in peristalsis showed a statistically significant positive correlation.

A review⁵⁹ of 86 papers pertaining to the action of atropine on the gastrointestinal tract disclosed that while much is known there is real need for clarification of the movements of the intestines and their response to drugs.

Experiments on a series of 9 trained dogs indicate that emotional stress as obtained by stimulation of a variety of somatovisceral and viscerovisceral reflexes does not result in polyrospasm, as is the prevalent opinion, but rather in an inhibition of the entire pyloric sphincter region (antrum, sphincter and bulb). Greater

53 Jacobson, L. O., and Palmer, W. L. The Effect of Anemia on Gastric Emptying, *Gastroenterology* **1**: 1133-1140, 1943.

54 Henschel, A., Taylor, H. L., and Keys, A. The Gastric Emptying Time of Man at High and Normal Environmental Temperatures, *Am J Physiol* **141**: 205-208, 1944.

55 Bourque, J. E., Jr., Friedman, M. H. F., Patterson, T., and Sandweiss, D. J. The Effect of Intravenous Injections of Urine Extracts on Gastric Motility, *Gastroenterology* **1**: 1049-1054, 1943.

56 Hoelzel, F. An Explanation of Appetite, *Am J Digest Dis* **11**: 101-108, 1944.

57 Wolf, S. The Relation of Gastric Function to Nausea in Man, *J Clin Investigation* **22**: 877-882, 1943.

58 McDonough, F. E., and Schneider, M. The Effect of Motion on the Roentgenographic Appearance of the Stomach and Small Bowel, *Gastroenterology* **2**: 32-45, 1944.

59 Henderson, V. E., and Sweeten, M. O. The Effect of Atropine on the Gastro-Intestinal Canal and Its Glands, *Am J Digest Dis* **10**: 241-247, 1943.

stimulation was required to produce inhibition after supradiaphragmatic vagotomy⁶⁰

Functional postoperative vomiting and periodic vomiting are attributed to spasm of the pylorus because the abdomen remains silent as long as the vomiting continues and peristaltic sounds recur within half an hour after the first administration of phenobarbital (luminal)⁶¹

Gastric Secretion—The volume of the gastric content was greatly decreased by both atropine sulfate and morphine sulfate, was unaffected by the sodium salt of dehydrocholic acid and was increased both by pilocarpine hydrochloride and neostigmine methylsulfate. The volume of the duodenal contents aspirated simultaneously was decreased by atropine sulfate and morphine sulfate, was practically unchanged by pilocarpine hydrochloride and was increased by neostigmine methylsulfate, the sodium salt of dehydrocholic acid and secretin. Atropine sulfate reduced the amount of acid secreted and entering the duodenum and the buffering value of the duodenal contents, but its action on the secretion of acid was apparently greater than its action on the secretion of bile, the secretion of pancreatic juice and the secretion of the duodenal mucosa. Morphine sulfate reduced the volume of the contents of the stomach and duodenum promptly and markedly. Glyceryl trinitrate and amyl nitrite did not reduce the duration of time during which bile was not found in the duodenal contents⁶²

Although it is generally believed that pilocarpine injected subcutaneously stimulates the mucus cells of the stomach very considerably but the parietal cells to only a slight extent, Hollander⁶³ found the opposite to be true.

Assays of the histamine activity extractable from the mucosa of various regions of the human stomach resected for peptic ulcer or carcinoma disclosed a yield from the fundic mucosa averaging 10.2 mg of histamine and 5.8 mg from the

antral mucosa⁶⁴. In only 3 cases were preparations of both fundic and central mucosa made from the same stomach, the differences were too small to be significant. There were no significant differences between the stomachs that secreted acid, as in peptic ulcer, and those that were achlorhydric, as in carcinoma.

Experiments to confirm the previously reported observation that secretagogues are more potent when applied to the gastric mucosa than when injected intravenously apparently show that they do not act by passing directly into the blood in an unchanged form but do act either in an altered form or by stimulating the elaboration of a gastric hormone⁶⁵.

Hallenbeck⁶⁶ investigated the effect of thymoxyethyldiethylamine and N-diethylaminoethyl-N-ethylamine on the normal gastric secretory process and found that the former did not inhibit the secretory response of Heidenham pouches to histamine nor significantly alter the response to methyl chloride. Both preparations inhibited the response to the ingestion of a meat meal. In an attempt to find the principle in yeast extract that stimulates gastric secretion, compounds known to be present in yeast, including choline chloride, beta alanine, glutathione and neurine bromide, were tested⁶⁷. Only neurine bromide was definitely active, producing an increase in volume and acidity. The increase in the first thirty minutes was comparable with that of histamine, but the effective dose was one hundred and fifty times greater, being 1.5 mg per kilogram. The effect of neurine, however, is much more prolonged, hence the response in terms of both volume and acid was more than double that of histamine. Nasio⁶⁸ studied the stimulating effect of prisco (a hydrochloride of 2-benzyl-4,5-imidazoline) on gastric secretion and found it to be superior to caffeine and alcohol when given orally and similar to histamine when given parenterally. No local or general reactions

60 Quigley, J. P., Bavor, H. J., Read, M. R., and Brofman, B. L. Evidence that Body Irritations or Emotions Retard Gastric Evacuation, Not by Producing Pylorospasm but by Depressing Motility, *J. Clin. Investigation* **22** 834-845, 1943.

61 Stevens, N. C. Functional Vomiting as Interpreted by Auscultation of the Abdomen, *New England J. Med.* **230** 753-754, 1944.

62 King, H. E., Comfort, M. W., and Osterberg, A. E. The Effect of Atropine Sulfate, Pilocarpine Hydrochloride, Prostigmine Methylsulfate, Sodium Salt of Dehydrocholic Acid and Secretin on the Gastric and Duodenal Acid and Duodenal Secretions of Normal Persons When Fasting, *Am. J. Digest. Dis.* **11** 31-40, 1944.

63 Hollander, F. The Secretion of Gastric Mucus and Hydrochloric Acid in Response to Pilocarpine, *Gastroenterology* **2** 201-211, 1944.

64 Trach, B., Code, C. J., and Wangenstein, O. H. Histamine in Human Gastric Mucosa, *Am. J. Physiol.* **141** 78-82, 1944.

65 Butler, D. B., Hands, A. P., and Ivy, A. C. Potency of Liver Extract in Stimulating Gastric Secretion by Intravenous Injection and by Direct Lavage, *Am. J. Physiol.* **139** 325-328, 1943.

66 Hallenbeck, G. A. Studies on the Effect of Gastric Secretion in Dogs, *Am. J. Physiol.* **139** 329-334, 1943.

67 Williams, E. F., Jr., Hoffman, C. F., and Nash, T. P., Jr. Stimulation of Gastric Secretion by Neurine, *Am. J. Physiol.* **139** 364-365, 1943.

68 Nasio, J. (a) A New Test for Gastric Function, *Rev. Gastroenterol.* **11** 174-178, 1944, (b) Una nueva prueba funcional gástrica la imidazolina, *Arch. argent. de enferm. d. ap. digest. y de la nutrición* **19** 49-56, 1944.

were noted. Roth and Ivy⁶⁹ confirmed the observation of earlier investigators that caffeine does not stimulate gastric secretion in the dog. However, when administered by the intravenous route or by lavage of the stomach caffeine does provoke a copious flow of acid gastric juice in the cat, and when administered intramuscularly or by the oral route in man it stimulates gastric secretion.

Davenport,⁷⁰ studying the secretion of iodide by the gastric mucosa, concluded that at a plasma concentration below 3 millimols per liter the gastric concentration of iodide is greater than that in the plasma whereas above 3 millimols it is equal to or lower than that in the plasma.

Vorobioff⁷¹ studied the psychogenic inhibition of gastric secretion, with apparently inconclusive results.

By the use of a Coup pouch dog, sodium bicarbonate has been found to increase the volume and the amount of acid in the gastric secretion during the hours immediately following the test meals, with a compensatory decrease during later hours.⁷² The feeding of moderate doses of aluminum hydroxide gel three times daily after a test meal results in no depression of secretory activity, either during or after the administration of the antacid.⁷³ Occasional increases in volume, total chloride, total base and free acid of the pouch secretion occur, but in the majority of experiments these increases are too small to be significant.

After gastroenterostomy and gastric resection only 37.4 per cent of 163 patients had a significant reduction in acidity, although 83.4 per cent had satisfactory clinical results.⁷⁴ In 75 patients who had no significant change in the gastric acidity following gastroenterostomy, 75 per cent nevertheless had satisfactory clinical results. Following gastric resection the reduction in acid was proportional to the extent of the resection.

69 Roth, J. A., and Ivy, A. C. The Effect of Caffeine upon Gastric Secretion in the Dog, Cat and Man, *Am J Physiol* **141** 454-461, 1944.

70 Davenport, H. W. The Secretion of Iodide by the Gastric Mucosa, *Gastroenterology* **1** 1055-1061, 1943.

71 Vorobioff, S. Los trastornos psicogenos inhibidores de la secrecion gastrica, *Arch argent de enferm d ap digest y de la nutricion* **19** 166-182, 1944.

72 Adams, W. L., Welch, C. S., and Clark, B. B. The Effect of Sodium Bicarbonate on Gastric Secretion, *Am J Physiol* **139** 356-363, 1943.

73 Adams, W. L., and Clark, B. B. The Effect of Aluminum Hydroxide Gel on Gastric Secretion, *Am J Physiol* **141** 255-258, 1944.

74 Heuer, G. J., and Holman, C. The Effect on Gastric Acidity of Gastroenterostomy and Gastric Resection for Peptic Ulcer, *Ann Surg* **118** 551-557, 1943.

However, of patients who had less than half the stomach resected only 25 per cent had a reduction in acidity and 90 per cent had satisfactory clinical results. In the opinion of Heuer and Holman such observations do not controvert the etiologic relationship between acid and ulcer but suggest that it may not be worth while to pursue the goal of achlorhydria by means of larger and larger resections. Perhaps it is better to accept the limitations of resection until a better operation is devised.

Diversion of the entire duodenal content to the stomach does not give effective neutralization, buffering or dilution of the gastric acidity in either the fasting or the digesting state.⁷⁵ Hence the slight and infrequent duodenal regurgitation occurring normally can scarcely be an essential factor in controlling intragastric acidity.

Enterogastrone concentrates administered parenterally and endogenous enterogastrone produced by the presence of fat in the intestine produce an inhibition of gastric secretion characterized by a moderate decrease in volume and acid concentration, thus causing a marked decrease in acid output.⁷⁶ Pepsin output is moderately depressed by enterogastrone in the absence of vagal influences.

Secretagogues do not act solely by absorption into the blood but cause the release of a hormonal gastric secretory agent. The peptic secretory response of a transplanted pouch to the hormonal stimulus of liver extract introduced into the stomach was not sufficient to cause a pronounced stimulation of pepsin secretion.⁷⁷ The results are interpreted as permitting the assumption that histamine could be the hormonal agent responsible for the secretion of pepsin.

Sodium alkyl sulfate decreases the peptic activity of the gastric contents in man when administered in adequate doses in conjunction with a diet low in lipids. The pepsin-inactivating action of sodium alkyl sulfate is inhibited in vitro by cream, butter, lecithin, glycerin and esters.

75 Kesavalu, A., and Mann, F. C. The Influence of Duodenal Contents on Intragastric Acidity. An Experimental Study, *Surgery* **14** 578-587, 1943. Braithwaite, L. R. The Role of Bile in Duodenal Regurgitation, *Brit J Surg* **31** 3-13, 1943.

76 Grossman, M. I., Greengard, H., Woolley, J. R., and Ivy, A. C. Pepsin Secretion and Enterogastrone, *Am J Physiol* **141** 281-288, 1944.

77 Grossman, M. I., Woolley, J. R., and Ivy, A. C. The Pepsin Content of Gastric Juice Secreted in Response to Hormonal Stimulation, *Am J Physiol* **141** 506-508, 1944. Barowsky, H., Upham, R., Dotti, L. B., and Kleiner, I. S. The Clinical Significance of the Concentration of Pepsin in Gastric Juice, *Rev Gastroenterol* **10** 201-204, 1943.

of fatty acids with carbon chains of varying lengths⁷⁸

After implantation in the stomach of a pedicle graft of the jejunal wall, a reversal of the normal secretory response to histamine was found in 4 of 5 dogs and a marked reduction in the fifth. The changes occurred within forty-five minutes and persisted at least four months.⁷⁹ In 2 animals after the transplant was resected the reaction to histamine returned to normal within one hour, though in 1 the fasting p_H remained slightly higher than before the transplant was made. In 5 of 6 dogs gastroenterostomy failed to prevent a marked diminution of the average p_H of the mucosa following the injection of histamine, but after conversion of the gastroenterostomy to a jejunal graft the normal response to histamine was reversed in all 6 dogs.⁸⁰ Transplants from the ileum and transverse colon were without effect in influencing the p_H of the gastric mucosa after administration of histamine, whereas after transplants from the duodenum and jejunum the p_H of the mucosa after histamine rose significantly.⁸¹ The effect was somewhat more pronounced in the jejunal grafts than it was in the duodenal. When 25 cc of saline washings of isolated jejunal loops were instilled into the stomachs of normal dogs and withdrawn after ten minutes, there followed a marked depression in the normal response of the gastric acidity to histamine, suggesting an inhibitory substance in the jejunal mucosa.⁸² In two later papers⁸³ these observations were amplified. The rationale of these procedures is very difficult for

the reviewers to understand. Teleologically there seems no reason to expect gastric secretion to be modified by an *external* secretion of the intestine. Ivy⁸⁴ has repeated and extended the work described by Andrus and his co-workers and has not been able to confirm it. Consequently, final appraisal must be withheld until further studies are made.

Gastroscopy—Schindler,⁸⁵ considering it essential to clarify the gastroscopic criteria of hypertrophic and atrophic gastritis, refutes the statements of Ruffin in 1940 that the characteristic signs of hypertrophic gastritis are influenced by inflation, shows that the role of inflation has been well studied and concludes that its effect on the folds cannot be used as evidence of gastritis. The prolonged vascular engorgement of rugae, causing them to become "intensely red, thick, and turgid," as produced by Wolf and Wolff experimentally, is not the picture of hypertrophic gastritis as it is seen gastroscopically. The gastroscopic criteria for both hypertrophic and atrophic gastritis are restated. In commenting on this paper Ruffin (page 363) raises the question of the gastroscopic appearance of the normal stomach, the effect of emotion and the clinical significance of the changes observed.

Renshaw,⁸⁶ considering the roentgenologic and gastroscopic examinations as supplemental and complementary rather than competitive, reviews their relative roles in 938 examinations on 842 patients. The gastroscopic examination was of primary value in the diagnosis for 25.6 per cent. For 17.7 per cent the diagnosis was established by gastroscopy when the roentgenogram was indeterminate, and for 7.9 per cent disease was excluded by gastroscopy when the roentgenogram was indeterminate. Gastroscopy was of secondary value for 55.4 per cent of the patients in that it merely confirmed the diagnosis already made or demonstrated an additional and minor condition. Gastroscopic examination was valueless for 19 per cent of the patients for various reasons, the most common being inability to visualize the area in question. The gastroscopic "blind areas" may be constant or inconstant, hence repetition of the gastroscopic examinations may be of as much value as repetition of the roentgen ray examinations. The accuracy on the

78 Kirsner, J. B., and Wolff, R. A. Effect of Sodium Alkyl Sulphate on Peptic Activity of Gastric Contents in Man and in Vitro, *Proc Soc Exper Biol & Med* **54**:11-13, 1943.

79 Stefko, P., Andrus, W. DeW., and Lord, J. W. The Effects of Jejunal Transplants on Gastric Acidity, *Science* **96**:208-209, 1942.

80 Andrus, W. DeW., Lord, J. W., Jr., and Stefko, P. Comparative Effects of Gastroenterostomy and Pedicle Jejunal Graft on the p_H of the Gastric Mucosa, *Proc Soc Exper Biol & Med* **52**:99-100, 1943.

81 Lord, J. W., Jr., Andrus, W. DeW., and Stefko, P. Comparative Effects of Pedicle Grafts from Different Levels of Intestinal Tract on p_H of Gastric Mucosa, *Proc Soc Exper Biol & Med* **52**:100-101, 1943.

82 Andrus, W. DeW., Lord, J. W., Jr., Stefko, P., and Dingwall, J. A., III. The Effect of Saline Washings of Isolated Jejunal Loops on Gastric Secretion, *Am J Physiol* **140**:287-290, 1943.

83 Andrus, W. DeW., Lord, J. W., Jr., and Stefko, P. Effects of Pedicle Grafts on Jejunum on the Wall of the Stomach on Gastric Secretion, *Ann Surg* **118**:499-522, 1943. A Possible Mode of Action of Pedicle Jejunal Grafts on Gastric Secretion as Indicated by Changes in p_H of the Surface of the Mucosa of the Stomach, *Am J Physiol* **141**:75-77, 1944.

84 Ivy, A. C. Personal communication to the authors, to be published.

85 Schindler, R. The Gastroscopic Picture of Hypertrophic and Atrophic Gastritis, *Gastroenterology* **2**:316-322, 1944.

86 Renshaw, R. J. F. Correlation of Roentgenologic and Gastroscopic Examinations from the Standpoint of the Gastroenterologist, *Am J Roentgenol* **5**:585-592, 1944.

first examination of the roentgenologic and the gastroscopic diagnosis for 170 patients is compared. For 109 patients, 64.1 per cent, the two methods were in agreement. For 15 the first roentgenologic examination was correct and the gastroscopic indeterminate. For 23 patients the gastroscopist made the first diagnosis. There were 14 patients for whom both methods were indeterminate and 9 patients, 5.3 per cent, for whom both were incorrect. Five per cent of gastric carcinomas are not detected by roentgenologic examination, and benign ulcers not penetrating the mucosa likewise escape detection.⁸⁷ Persistent spasm of the antrum taxes the diagnostic acumen of the roentgenologist more than any other condition. A patient considered roentgenologically to have a neoplasm of the antrum with metastasis to the right lung was shown gastroscopically to have a normal stomach. The pulmonary lesion was then diagnosed as a tuberculoma. The patient remained well for over three years. Benedict,⁸⁸ in a critical review of gastroscopy, expresses the opinion that examination of the stomach should be done before gastroscopy. Pierson and Pack⁸⁹ recommend the vertical position of the patient for gastroscopic examination because it seems to permit better visualization of the fundus and cardia and hence may help to disclose more of the early resectable lesions.

Rafsky⁹⁰ combined gastrophotographic studies in natural colors with gastroscopy in the examination of 41 patients. For 26 of the 41 patients the gastrophotographic findings corresponded with the endoscopic findings, but for the other 15 the gastrophotographs did not record the endoscopic findings. For 11 the photographs were blurred because of mucus in the stomach. For 4 the gastric wall was clearly outlined, but the lesion was not visualized because the patient moved or the depth to which the instrument was inserted was miscalculated. The combined examination was considered helpful in the differential diagnosis of benign and of malignant lesions of the stomach, as the contrast on the photographs was distinct. Gastrophotography

served as a check on gastroscopy by furnishing a permanent record.

Gastritis — Schindler⁹¹ studied the correspondence between the gastroscopic findings and the histologic structure of the stomach obtained by biopsies and resections. The surface epithelium of the stomach in the normal state is carefully described, as well as that in chronic superficial gastritis, atrophic gastritis and hypertrophic gastritis. Two kinds of metaplasia were found in atrophic gastritis: (1) the metaplasia of the epithelium of the surface and of the pits into an intestinal type and (2) the metaplasia of the true body glands into a pyloric type of mucus-forming glands. In the hypertrophic form of gastritis, Schindler found the mucosa to be thickened by interstitial infiltration, by extensive proliferation of the surface epithelium or by an enormous increase of the glandular apparatus. Gitlitz and Colp⁹² undertook to determine whether any histologic alterations occurred in the wall of the stomach during resection by making a biopsy at the beginning of the operation and comparing it with the resected specimen. No changes of significance were observed in 35 such observations.

Atrophic gastritis may be a deficiency state, particularly of the vitamin B complex.⁹³ The results of treatment of 5 patients with large doses of thiamine hydrochloride, nicotinamide, riboflavin, pantothenic acid, paraaminobenzoic acid and vitamin A are described. No significant changes in the gastric mucosa as determined by gastroscopic examination were seen, although in 2 of the 5 patients disappearance of the atrophic changes was noted when treatment with choline chloride was given. Further observation will be required to evaluate the effect of choline. Layne and Carey⁹⁴ produced black tongue nine times in 5 dogs by means of the Goldberger diet. Severe inflammation of the mucosa of the mouth was not accompanied with similar changes in the gastric mucosa or with significant change in the gastric secretion. Mild hyperemia of the mucosa and decreased tonus were observed early in the experiment. Pallor then developed in all

87 Cohn, A. L., and Levitin, J. Problems in Gastric Diagnosis. The Gastroscope as an Aid to X-Ray Examination, *Gastroenterology* **1** 841-854, 1943.

88 Benedict, E. B. (a) A Critical Review of Gastroscopy, *Bull. New York Acad. Med.* **20** 179-189, 1944, (b) Medical Progress—Endoscopy, *New England J. Med.* **230** 642-647 and 669-676, 1944.

89 Pierson, J. C., and Pack, G. T. Indications for Vertical Gastroscopy, *Rev. Gastroenterol.* **11** 111-113, 1944.

90 Rafsky, H. A. Gastrophotography in Natural Colors in Conjunction with Gastroscopy, *Am. J. M. Sc.* **206** 618-622, 1943.

91 Schindler, R. The Surface Epithelium of the Normal and Inflamed Stomach, *Gastroenterology* **2** 233-249, 1944.

92 Gitlitz, A. J., and Colp, R. Gastric Histology and Subtotal Gastrectomy, *Ann. Surg.* **118** 523-550, 1943.

93 Shapiro, N., Schiff, L., Bloch, H. S., Garber, E. S., and Hannaher, M. J. Some Observations on Specific Vitamins and Atrophic Gastritis, *Gastroenterology* **2** 121-132, 1944.

94 Layne, J. A., and Carey, J. B. The Effect of a Blacktongue-Producing Diet upon the Endoscopic Appearance of the Gastric Mucosa in the Dog, *Gastroenterology* **2** 133-137, 1944.

except 1 of the animals, but there was no characteristic gross or microscopic alteration

Gordon⁹⁵ reviews the problem of correlation between symptoms and findings in gastritis, indicates the wide variety of opinions experienced and reports on his own series of 78 patients with gastritis, 15 with the hypertrophic type, 8 with the superficial and atrophic, 41 with the superficial and 14 with the atrophic. Five types of symptoms were noted: acute attacks of pain with or without hemorrhage, a syndrome resembling peptic ulcer, early postprandial distress, a syndrome of constitutional inferiority and a syndrome resembling primary anemia. Gordon thinks there are two fairly distinct gastroscopic and clinical entities: hypertrophic gastritis, with symptoms resembling those of peptic ulcer, and atrophic or superficial gastritis, with symptoms of general weakness, numbness and tingling, frequent soreness of the mouth and often achlorhydria.

Browne and McHardy,⁹⁶ in evaluating the cases in which a subtotal gastrectomy fails to reveal digestive distress, emphasize the importance of gastroscopic examination as the only satisfactory method of studying the gastric mucosa and of making a diagnosis of postoperative gastritis. The therapeutic regimen suggested consists of a high protein, relatively bland diet approximating 4,000 calories a day supplemented by the parenteral administration of vitamins B and C and liver extract, together with the use of aluminum hydroxide and an antispasmodic.

Annis⁹⁷ performed gastroscopic examination on 276 of 2,142 patients with gastrointestinal disease seen at Camp Blanding, Florida, and found some form of gastritis in 109 (39.5 per cent), hypertrophic changes, in 52, superficial changes in 44, and atrophic changes, in 13. The observed gastroscopic change did not correspond with any definite clinical history. The diagnosis of psychoneurosis was made by the psychiatrist much more commonly for persons with chronic dyspepsia with a normal gastric mucosa than for persons with gastritis. Therapy was not of definite value, as judged either by the clinical course or by the results of gastroscopic examination. Annis is convinced "that the patient with chronic gastritis is likely to be a military disability. Indeed it is hard to think of a form of chronic dyspepsia,

organic or functional, which does not prevent the individual from becoming an effective field soldier." Guyer⁹⁸ compared the roentgenologic and gastroscopic findings on 200 consecutive dyspeptic soldiers in the British Army. The roentgenologic analysis was as follows: normal, 73.5 per cent, duodenal ulcer, 8.5 per cent, duodenitis, 7.5 per cent, gastric ulcer, 3.5 per cent, gastritis, 2.5 per cent, other findings, 4.5 per cent. The gastroscopic analysis yielded the following results: normal, 47 per cent, gastritis (all types), 44 per cent, gastric ulcer, 3.5 per cent, healed gastric ulcer, 4.5 per cent, adenoma, 0.5 per cent. In an analysis of 61 cases of gastritis it was found that in 29.5 per cent the disease was of the mild superficial type, in 45.9 per cent, of the severe active superficial type, in 19.6 per cent, of the atrophic type, and in 4.6 per cent, of the hypertrophic type. It was very noticeable that nearly all the patients said they had suffered from dyspepsia in civil life but had been able to carry on with their occupations as long as they were in a position to have the type of diet which suited their individual requirements. Alkalis had been prescribed medically or had been purchased spontaneously by practically every one. Symptoms were uniform, consisting of a complaint of indefinite epigastric pain, generally after meals, relieved by vomiting. The striking feature in all cases was the poor mental outlook and the state of general depression with complaints of weakness, headaches and inability to compete with others during their military training.

Feldman⁹⁹ reports a most unusual case of hypertrophic gastritis with giant gastric rugae producing a filling defect suggestive of carcinoma roentgenologically.

A fatality occurred after use of tetracaine hydrochloride (2 per cent) as an anesthetic gargle in preparation for gastroscopic procedures on a patient with carcinoma of the esophagus and extensive metastases to the liver.¹⁰⁰

Hypertrophic Pyloric Stenosis—Two cases of hypertrophic pyloric stenosis are reported because of the rarity of the condition in adults and because of the possibility that psychogenic fac-

98 Guyer, R. B. The Comparison of Radiological and Gastroscopic Findings in 200 Dyspeptic Soldiers, *Brit J Radiol* 16:241-246, 1943.

99 Feldman, M. Giant Gastric Rugae with Diffuse Hypertrophic Gastritis. A Case Resembling a Neoplasm on the Lesser Curvature of the Stomach, *Radiology* 41:181-183, 1943.

100 Hansen, F. M., Jr., and Stealy, C. L. Sudden Death Following the Use of Pontocaine as a Gargle Anesthetic for Gastroscopic Examination, *Rev Gastroenterol* 10:212-213, 1943.

95 Gordon, W. The Symptoms Associated with Chronic Gastritis, *Gastroenterology* 1:1013-1021, 1943.

96 Browne, D. C., and McHardy, G. Postgastrectomy Gastritis, *Ann Int Med* 20:789-792, 1944.

97 Annis, J. W. Gastritis in the Military Service, *Gastroenterology* 2:85-92, 1944.

tois may play an etiologic role¹⁰¹ Both patients were aggressive, ambitious and driving, and both were beset by social and financial problems When confronted with distressing situations which would arouse anxiety in a normal person, both of them were conscious of somatic distress The patients gave a comparatively brief ulcer-like history with symptoms of partial pyloric obstruction Gastric resection was done on both because carcinoma could not be excluded Pathologic examination disclosed hypertrophic muscle and infiltration of the stomach with plasma cells suggesting gastritis although the gastroscopic examination revealed nothing abnormal Wakefield¹⁰² describes the case of a 52 year old white man with painless nausea and vomiting for thirty years until cured by resection of a hypertrophied pylorus Vance¹⁰³ gives a brief but comprehensive review of 27 cases of congenital pyloric stenosis

Foreign Bodies—Benedict¹⁰⁴ reports on a 3 year old girl who swallowed an open safety pin and then, while awaiting operation, vomited the pin Jenkins¹⁰⁵ describes a soldier who had vague biliary symptoms of only thirty-six hours' duration At operation a gangrenous, perforated gallbladder impacted with over 200 stones, complete fibrous obliteration of the cystic and common bile ducts, fibrous obliteration of the distal portion of the hepatic duct and general peritonitis were found After complete postoperative recovery, the hepaticogastric fistula was demonstrated roentgenographically two months later

Syphilis—A case of well proved extensive secondary syphilis is noteworthy primarily because of the gastroscopic studies¹⁰⁶ "The mucosa was hyperemic and edematous throughout There were numerous submucosal hemorrhages of all sizes and shapes A few superficial erosions were seen and there was much adherent mucus The impression was that of a chronic superficial gastritis" A month later "no mucosal hemorrhages were seen The anterior and posterior wall together with the lesser and greater curvatures presented a dull mucosa This dullness

was patchy On the anterior wall of the body of the stomach the mucosa presented a patchy, gray, thin appearance, and some large submucosal blood vessels were visible The chronic superficial gastritis was present at this time" Unfortunately, a later examination was not possible The evidence that the changes noted were due to syphilis is presumptive

Actinomycosis—Shearburn¹⁰⁷ reports proved actinomycosis of the stomach with duodenal ulcer asymptomatic for eighteen months It is the only case found in the literature in which the patient lived more than one year after operation A case of subphrenic actinomycotic abscess with persistent infection is also reported and presumed to be the result of actinomycotic infection resulting from perforation of a peptic ulcer In neither case was it possible to prove whether the mycosis was the primary cause of the ulcer or whether there was a secondary invader

Fibrosis—Under the heading of gastric fibrosis involving the duodenum, Silverman and Friedman¹⁰⁸ describe the case of a 40 year old white man who complained of intermittent pain in the epigastric area for fourteen years, with periods of remission, the epigastric pain was sharp, occasionally radiating to the infracapsular area bilaterally and to the midline on the same level, sometimes it was so severe that it awakened him at night Ingestion of food relieved the pain for about an hour The roentgenologic examination showed what appeared to be a polyp in the duodenal cap and a more irregular filling defect in the first portion of the duodenum, the walls of which were extrinsically smooth and well rounded Gastric resection was performed On microscopic examination extensive fibrosis of the submucosa was found, extending between the muscle bundles and including the subserosal surface of the stomach No malignant cells were identified The case is presented as an instance of localized fibrosis of the stomach and duodenum The history, however, is that of peptic ulcer, the photographs suggest the presence of a deformity of the ulcer type at the junction of the first and second portions of the duodenum, at operation "a stellate scar was found on the anterior surface of the duodenum" thought to be the site of an old ulcer, and hence one wonders if the fibrosis may not have been secondary to a duodenal ulcer or, perhaps, to additional healed gastric ulcers

101 Berk, E, and Dunlap, H J Hypertrophic Pyloric Stenosis in Adults, *Ann Surg* **119** 124-133, 1944

102 Wakefield, H Hypertrophic Pyloric Stenosis in Adults, *Gastroenterology* **2** 250-257, 1944

103 Vance, C A Congenital Pyloric Stenosis, *Ann Surg* **119** 351-359, 1944

104 Benedict, E B Vomiting of an Open Safety Pin, *New England J Med* **230** 484, 1944

105 Jenkins, H B Spontaneous Hepatogastric Biliary Fistula, *J A M A* **123** 830-832 (Nov 27) 1943

106 Spellberg, M A, and Norfleet, W J Early Gastric Syphilis, *Gastroenterology* **2** 191-194, 1944

107 Shearburn, E A Actinomycosis of the Stomach and Duodenum Report of Two Cases, *Surgery* **14** 38-46, 1943

108 Silverman, D N, and Friedman, L L Gastric Fibrosis Involving the Duodenum, *Gastroenterology* **2** 186-190, 1944

Surgery for Functional Disturbances—Subtotal gastrectomy was done in 1 case and resection of the ascending colon in another by Strelinger¹⁰⁹ for gastrointestinal disease of uncertain nature, with the argument that in exceptional circumstances such a procedure is justifiable. The cases presented are not convincing.

PEPTIC ULCER

Historical—Goldstein¹¹⁰ gives an interesting and well illustrated account of ulcer and cancer in the Middle Ages.

Incidence—Tidy¹¹¹ studied the crude death rates during the period 1912 to 1938 for peptic ulcer in various districts in the British Isles and found little or no rise in the years between 1912 and 1920, a rapid rise between 1921 and 1930 and no further rise between 1930 and 1938.

Etiology—Davidoff¹¹² reports 12 more cases of coexistent lesions of the central nervous system and the gastrointestinal tract.

In a discussion of the pathologic physiology of gastric and duodenal ulcer, Shay¹¹³ presents the results of a thorough study made by him and his associates of the gastric, motor and secretory functions in normal human subjects and in patients with peptic ulcer, emphasizing the role of local gastric and duodenal mechanisms. The introduction into the duodenum of hydrochloric acid, hypertonic saline solution, hypertonic dextrose solution, olive oil and cream inhibited gastric secretion. These results are more pronounced in normal persons and in persons with healed duodenal ulcer than in patients with active ulcer, thus leading Shay to suggest that the return of gastric motor and secretory functions to normal is probably the only reliable criterion of healing in a duodenal ulcer. The therapeutic value of milk and cream in the ulcer diet probably rests in part on the inhibitory effect of fat. Glaessner,¹¹⁴ on the basis of the stimulation of gastric inhibitory secretion by insulin and the inhibition of gastric secretion resulting from

the injection of dextrose into the duodenum or jejunum, argues for a very important connection between gastric secretion and blood sugar in which hepatic function plays an important role. He interprets the rarity of peptic ulcer (0.25 per cent) in diabetic persons and the frequency of achlorhydria (33.3 per cent) as further evidence. The mechanism of the stimulation of the gastric secretion by insulin is not clear, but the inhibition from the intraduodenal administration of dextrose is apparently that elaborated by Shay.

McHardy and Browne¹¹⁵ report 2 cases of duodenal ulcer developing apparently after so-called "histamine desensitization" and thought to afford clinical confirmation of the experimental production of peptic ulcer with histamine. This is in contrast to Horton's report of healing during the process of "desensitization." McHardy and Browne consider Horton's evidence insufficient and more than offset by the 2 cases described by them.

The same authors describe a pair of identical twins in whom duodenal ulcer developed at identical periods in their lives.¹¹⁶ This observation is thought to add weight to the theory of "constitutional predisposition." Bearing on this same topic is the report¹¹⁷ of a familial history of digestive disease in 340 (21.8 per cent) of 1,617 patients with duodenal ulcer and 636 patients with gastric ulcer, from which it is concluded that there is no familial predisposition in the localization of peptic ulcer. Boros,¹¹⁸ on the other hand, argues for a constitutional predisposing factor because of a family of eleven children in which the mother, four of the nine sons and one of the two daughters all had ulcer with massive hemorrhage, as did the daughter of the eldest son. In the opinion of the reviewers, papers of this type would be improved by a study such as Barnett's statistical analysis of the familial incidence of anacidity.¹¹⁹

The diets of 16 patients with chronic ulcer were found to be poorly balanced and deficient in food energy value as well as in thiamine and ascorbic acid.¹²⁰

109 Strelinger, A. Major Resection for Functional Gastrointestinal Disease. Report and Evaluation of Two Cases, *Am J Surg* **62** 72-79, 1943.

110 Goldstein, O. I. Ulcer and Cancer of the Stomach in the Middle Ages, *J Internat Coll Surg* **6** 482-490, 1943.

111 Tidy, H. Course of Death Rate from Peptic Ulcer in Great Britain, 1912-1938, *Brit M J* **1** 677-682, 1944.

112 Davidoff, L. M. The Influence of the Nervous System on the Gastro-Intestinal Tract, *Rev Gastroenterol* **11** 102-105, 1944.

113 Shay, H. The Pathologic Physiology of Gastric and Duodenal Ulcer, *Bull New York Acad Med* **20** 264-291, 1944.

114 Glaessner, C. L. Gastric Secretion and Sugar Metabolism, *Am J Digest Dis* **10** 307-313, 1943.

115 McHardy, G., and Browne, D. C. Duodenal Ulcer Developing in Man Following "Histamine Desensitization," *Gastroenterology* **2** 345-347, 1944.

116 McHardy, G., and Browne, D. C. Duodenal Ulcer Concomitant in Identical Twins, *J A M A* **124** 503 (Feb 19) 1944.

117 Bonorino Undaondo, C., and Nasio, J. La herencia en la ulcera gastrica y duodenal, *Prensa med argent* **31** 223-233, 1944.

118 Boros, E. Familial Peptic Ulcer Hemorrhage, *Am J Digest Dis* **11** 45-47, 1944.

119 Bloomfield, A. L., and Polland, W. S. Gastric Anacidity, New York, The Macmillan Company, 1933, p. 59.

Collins¹²¹ made a detailed study of gastric glands in 13 surgically resected stomachs. Degeneration, necrosis and repair were observed in stages of gradually increasing severity and magnitude, suggesting a single disease process. The most minimal changes were scattered glands lined with epithelial cells not differentiated into chief and parietal cells, together with scattered glands containing cells undergoing a process of vacuolar degeneration. These changes were thought to be compatible with the normal process of degeneration and repair. Degeneration was sometimes associated with infiltration of polymorphonuclear leukocytes, perhaps involving a number of adjacent glands and resulting in focal necrosis. The most advanced stage was ulceration and scarring involving all the layers of the stomach. When the degeneration was overwhelming and the repair inadequate, peptic ulcer resulted. When the degeneration was long continued with exhaustion of the germinal epithelial cells, atrophic gastritis resulted. The paper is reminiscent of earlier workers in this country and abroad, notably those of Konjetzny and Puhl.

Nedzel¹²² considers the "spasm theory" of peptic ulcer to be the most logical one to explain the periodicity of the lesion. Experiments consisting of the administration of a single injection or repeated injections of pitressin intravenously were made on 62 dogs. Negative results were obtained in 39 (63 per cent) and positive results in 23 (37 per cent). The latter group showed lesions of the stomach and duodenum ranging from a small erosion to a large ulcer. Direct observation through an incision of the abdomen and stomach to observe the effect of the pitressin disclosed contraction of the stomach and the formation of petechial hemorrhages. "For about thirty to forty-five minutes, especially after two or three injections of pitressin, the small hemorrhages definitely began to resemble small erosions and the mucosa became hyperemic with the folds disappearing."

In a further study, Lord, Andrus and Stefko¹²³ used the histamine and beeswax technic for the production of peptic ulcer. In 2 normal control dogs given 120 mg of histamine daily for

thirty days multiple erosions of the duodenum developed, whereas 2 dogs with jejunal transplants similarly treated were found at necropsy to have normal gastrointestinal tracts. Six normal dogs and 1 with a jejunal transplant were then given histamine daily and observed for seven weeks. In all the 6 normal dogs hyperemia of the duodenum developed, in 3, ulcerations extending into the muscularis, and in 3, multiple erosions. The dog with the jejunal transplant was found at autopsy after the seven weeks to have a normal stomach and duodenum. One of the animals given histamine began to have tarry stools on the eighth day and was operated on on the twelfth day. A duodenotomy disclosed several punctate erosions. A jejunal transplant to the stomach was carried out. On the twenty-sixth postoperative day autopsy revealed a normal gastric and duodenal mucosa, even though the daily administrations of histamine had been continued. The lesions produced in the control animals do not appear to the reviewers to have been of a magnitude comparable with those produced by others using this technic. Hence the influence of the jejunal transplant is difficult to assess. Furthermore, as mentioned earlier, Ivy has not been able to confirm the alleged inhibitory effect of jejunal transplants on gastric secretion.

Ivy,¹²⁴ in discussing recent experimental developments pertaining to the clinical management of peptic ulcer, reports on pyrogen-free preparations of enterogastrone which prevented the development of peptic ulcer in Mann-Williamson dogs. Furthermore, the animals failed to have ulcer for at least one year after treatment was discontinued. The enterogastrone preparation does not depress the gastric secretion of acid or pepsin in response to an alcohol test meal, although it does greatly reduce the excessive continued fasting secretion. Ivy advances the hypothesis that enterogastrone increases the resistance of the jejunal mucosa to ulceration. In 15 patients with two or more recurrences of peptic ulcer annually, palliative results were obtained by the administration of the enterogastrone preparation. Sandweiss¹²⁵ similarly reports that the principle in urine described by him as possessing prophylactic and therapeutic properties against Mann-Williamson ulcers immunizes against the formation of ulcer. In 6 Mann-

120 Riggs, H. E., Reinholt, J. G., Boles, R. S., and Shore, P. S. The Diet and Chronic Peptic Ulcer, *J. A. M. A.* **124** 639-641 (March 4) 1944.

121 Collins, V. P. The Peptic Ulcer and Chronic Gastritis, *Ann. Surg.* **118** 1005-1014, 1943.

122 Nedzel, A. J. Experimental Production of Gastric Ulcers in Dogs by Inducing Vascular Spasm with Pitressin, *Am. J. Digest. Dis.* **10** 283-296, 1943.

123 Lord, J. W., Jr., Andrus, W. DeW., and Stefko, P. L. Effects of Jejunal Transplants on Experimental Production of Peptic Ulcers, *Arch. Surg.* **46** 459-464 (April) 1943.

124 Ivy, A. C. Some Recent Developments in the Physiology of the Stomach and Intestine Which Pertain to the Management of Peptic Ulcer, *Bull. New York Acad. Med.* **20** 5-14, 1944.

125 Sandweiss, D. J. The Immunizing Effect of the Anti-Ulcer Factor in Normal Human Urine (Anthelone) Against the Experimental Gastrojejunal (Peptic) Ulcer in Dogs, *Gastroenterology* **1** 965-969, 1943.

Williamson dogs given intramuscular injections of from 1 to 5 mg of the antiulcer substance (not urogastrone) in normal human urine daily for a period of one year or longer ulcers failed to develop eleven months after therapy was withdrawn (1 mg represented 60 cc of urine). This is interpreted as a long-standing immunity not due to depression of gastric secretion. The name "anthelone" (Greek *ἀντί* against, *ἔλκος* ulcer) is proposed for the substance described in order to differentiate it from the urogastrone factor, which does inhibit gastric secretion and motility. This approach to the problem of the therapy of peptic ulcer is intriguing in its possibilities, and hence the results of further study are eagerly awaited.

Trauma—Fowler¹²⁶ estimates the incidence of primary ulcer resulting from a single blunt trauma at 0.6 per cent and presents 9 litigated cases in which peptic ulcer allegedly was due to trauma. The verdicts were equally divided, with 1 compromise. In the opinion of Fowler there are a few cases in which fresh lesions revealed at operation or autopsy may undeniably be of primary traumatic origin, but more frequently such an origin cannot be proved. Furthermore, a pre-existing ulcer may be reactivated by direct abdominal trauma or indirectly by neurosis resulting from the injury. Kinmonth¹²⁷ reports the interesting case of a 15 year old boy crushed between two wagons who at operation was found to have a laceration 3 cm long in the anterior wall of the stomach involving the seromuscular layers only, and half a pint (0.25 liter) of blood in the left infracolic compartment due to a complete tear in the mesentery of the small intestine. The patient three weeks later had melena and hematemesis. At the second operation an ulcer somewhat larger than a sixpence was found in the center of the site of the injury with several small bleeding vessels in the floor of the ulcer.

Roentgenology—Feldman,¹²⁸ in discussing the problem of the roentgenologic diagnosis of duodenal ulcer in inductees, stresses the early mucosal changes. Borman,¹²⁹ commenting on the infrequency of peptic ulcer in the descending duodenum and the rarity with which it is diagnosed roentgenologically, attributes the error of the roentgenologist to inadequate study of the

duodenum and to failure in differentiating the lesion from diverticula or barium sulfate retained in the lateral recess of a deformed duodenal bulb. Seven cases are reported of active ulcer in the upper descending duodenum, located on the upper and inner margin of the descending duodenum usually just below the superior flexure, with secondary spasm, mucosal distortion and medial retraction of the adjacent upper descending duodenum. Hemorrhage was a prominent feature in 6 of the cases and nocturnal pain in 4. Kahlstrom¹³⁰ reports a duodenal ulcer measuring 5 by 4 cm at autopsy. Two interesting cases of benign ulcer with decided shortening of the lesser curvature of the stomach are described.¹³¹ Preiss¹³² reports a benign ulcer of the greater curvature, with excellent roentgenograms and histologic confirmation. Señorans¹³³ describes a similar lesion observed gastroscopically and roentgenologically over a period of nine months, with complete healing.

Illustrating the variety of disease seen in one person, Moreno¹³⁴ reports the case of a 55 year old man with pulmonary and laryngeal tuberculosis who had had a tuberculoma of the cecum removed, eleven years later carcinoma of the flexure followed. Three years later a benign gastric ulcer with gastritis developed.

Treatment—Portis¹³⁵ discusses the clinical significance of emotional disturbances as well as organic factors in the development of gastritis, duodenal irritation and duodenal ulcer and urges evaluation of both the somatic and the psychologic factors in their treatment. Bolen,¹³⁶ in a study of 40 patients, emphasizes the importance of relieving emotional stress and hence concludes that mental anxiety and strain play an important role in the causation of peptic ulcer. Winkel-

130 Kahlstrom, S. C. Giant Ulcer of the Duodenum. *M. Bull. Vet. Admin.* **20**: 451-452, 1944.

131 Señorans, A. J., Gñi Moreno, I., and Aguirre, J. A. Desplazamiento y fijación plástica de vísceras por úlceras escleroretrotráctiles del estómago, *Arch. argent. de enferm. d. ap. digest. y de la nutrición* **19**: 13-35, 1944.

132 Preiss, A. A Case of Peptic Ulcer on the Greater Curvature of the Stomach, *Brit. J. Radiol.* **17**: 182-184, 1944.

133 Señorans, A. J. Úlcera gástrica de la curvatura mayor, *Arch. argent. de enferm. d. ap. digest. y de la nutrición* **18**: 533-545, 1943.

134 Moreno, J. Sobre interpretación radiológica de una úlcera gástrica: tratamiento médico, *Arch. argent. de enferm. d. ap. digest. y de la nutrición* **19**: 150-165, 1944.

135 Portis, S. A. The Clinical Significance of Emotional Disturbances Affecting the Stomach, Duodenum and Biliary Tract, *Psychosom. Med.* **6**: 71-73, 1944.

136 Bolen, H. L. The Emotional Factor in Peptic Ulcer, *Rev. Gastroenterol.* **10**: 187-191, 1943.

126 Fowler, R. H. External Trauma and Peptic Ulcer, *Indust. Med.* **12**: 614-632, 1943.

127 Kinmonth, J. B. Abdominal Injuries Leading to Gastric Ulceration and Haematemesis in a Boy of 15, *Brit. J. Surg.* **31**: 93-94, 1943.

128 Feldman, M. Responsibility of the Roentgenologist in the Wartime Duodenal Ulcer Problem, *Radiology* **42**: 356-358, 1944.

129 Borman, C. N. Ulcer in Descending Duodenum, *Am. J. Roentgenol.* **50**: 752-764, 1943.

stem,¹³⁷ in reviewing the various treatments of peptic ulcer, rates the continuous intragastric drip of milk and soda as the best type of medical therapy and partial gastrectomy combined with vagotomy as the most valuable form of surgical treatment. Driscoll and Aaron¹³⁸ present a series of 100 cases of peptic ulcer treated by fourteen different acceptable methods. Relief was obtained in 81 of the 100 cases. Hence the conclusion was reached that except for cases of complicated or intractable ulcer any treatment will give results provided it is followed intelligently. "Successful treatment depends upon co-operation of the physician and the patient, and the control of gastric acidity by diet and antacids." The *in situ* action of the antacids was studied in 17 patients with duodenal ulcer by means of intubation of the first portion of the duodenum, and it was found that while the oral administration of an antacid in the usual therapeutic dose does reduce the acidity of the contents of the first part of the duodenum the reduction is neither great nor long lasting and may be followed by a rebound increase.¹³⁹

Demole and Guye¹⁴⁰ used the synthetic adrenal substance desoxycorticosterone in the treatment of about 40 patients with ulcer. Pain disappeared after the second or third injection, even in patients who had been resistant to ordinary treatment. The characteristic roentgenologic appearance was completely altered in fifteen or more days. Only 1 of the patients failed to respond. The late results of desoxycorticosterone therapy were not so favorable as the immediate effects, particularly in case of chronic ulcer. There was only 1 with permanent result among 11 patients with old ulcers. Of 10 patients who had the ulcer for less than a year, 8 were permanently cured. In general, a relapse followed after from four to ten months in more than half of the patients.

Metz and Lackey¹⁴¹ report "satisfactory clinical results" in 74 per cent of 418 unselected patients with uncomplicated peptic ulcer treated with intranasal insufflation or desiccated posterior pituitary powder as a supplement to "rational medical management."

Fogelson and Shoch¹⁴² have studied the treatment of gastroduodenal ulcerative disease with sodium alkyl sulfate, with the thought that inactivation of pepsin rather than alteration of gastric acidity might permit healing of the ulcer. Of the numerous substances belonging to the large group of detergents investigated for their ability to inhibit peptic activity in dilute concentration without altering acidity, sodium alkyl sulfate was found to be one of the most effective and most available. When this substance was fed at intervals of ten hours in doses of 0.1 Gm to dogs given daily injections of histamine and beeswax, the survival time of the dogs was prolonged to well over two hundred days in approximately half of the animals. This survival period was attributed to inactivation of the pepsin. As a control the authors accepted the observation of others that the survival period of such dogs is not over thirty days. Sodium alkyl sulfate was shown to be nontoxic to dogs when given in doses of 2 Gm a day for ten months and when given to human beings in a dose of 1 Gm daily for eight weeks. The clinical study consisted in the administration of sodium alkyl sulfate in doses of 0.2 Gm apparently at hourly intervals although not specifically stated. In a series of 34 patients with ulcer considered "intractable," there were 26 who had satisfactory results and 8 for whom failure resulted. "In most of the patients responding to sodium alkyl sulfate there was marked improvement within ten days although no result was classified as a failure until the treatment had been given a thirty day trial."

Steigmann and Marks¹⁴³ were unable to confirm the alleged lowering of peptic activity in the presence of an unaltered p_H . The antacids calcium carbonate, aluminum hydroxide and magnesium hydroxide caused a more pronounced inhibition than did the detergent. The clinical use of sodium lauryl sulfate failed to reveal any superiority over the other medications used. The pepsin-inactivating action of sodium alkyl sulfate is inhibited *in vitro* by cream, butter, lecithin, glycerin and esters of fatty acids with carbon chains of varying length.¹⁴⁴ Kirsner and Wolff¹⁴⁵

137 Winkelstein, A. The Modern Treatment of Peptic Ulcer, *Bull New York Acad Med* **20** 87-98, 1944

138 Driscoll, E. F., and Aaron, A. H. Response to Treatment of Peptic Ulcer, *New York State J Med* **44**:266-269, 1944

139 Berk, J. E., Rehfuess, M. E., and Thomas, J. E. *In Situ* Effects of Antacids in Duodenal Ulcer, *Arch Int Med* **72** 46-57 (July) 1943

140 Demole, M., and Guye, P. La cortine dans le traitement de l'ulcère gastro-duodénal, *Praxis* **32** 517-519, 1943

141 Metz, M. H., and Lackey, R. W. Peptic Ulcer Treated with the Aid of Posterior Pituitary Extract, *South M J* **36** 747-750, 1943

142 Fogelson, S. J., and Shoch, D. E. Treatment of Gastroduodenal Ulcerative Disease with Sodium Alkyl Sulfate, *Arch Int Med* **73** 212-216 (March) 1944

143 Steigmann, F., and Marks, A. R. Inhibition of Peptic Activity in the Treatment of Peptic Ulcer, *Am J Digest Dis* **11** 173-178, 1944

144 Kirsner, J. B., and Wolff, R. A. Effect of Sodium Alkyl Sulfate on Peptic Activity of Gastric Contents in Man and *In Vitro*, *Proc Soc Exper Biol & Med* **54** 11-13, 1943

145 Kirsner, J. B., and Wolff, R. A. Effect *In Vitro* of Various Detergents on Peptic Activity of Human Gastric Content, *Gastroenterology* **2** 270-273, 1944

in further *in vitro* studies found a number of anionic detergents which do not inhibit peptic activity, two which have a moderate effect and two, Duponol PC and Naccanol E, both anionic detergents, which inhibit peptic activity as decidedly and as effectively as commercial sodium alkyl sulfate. In a carefully conducted clinical study¹⁴⁶ in which sodium alkyl sulfate was administered together with milk and cream, hourly doses of 130, 260, 390 and 520 mg did not produce a lowering of peptic activity. However, when the sodium alkyl sulfate was given in doses of 780 mg (1) at hourly intervals with a low fat diet there was an appreciable, although temporary, decrease. No toxic effects except mild diarrhea were noted. Kirsner and Wolff¹⁴⁷ apparently used three to five times as much sodium alkyl sulfate as reported by Fogelson and Shoch. No beneficial effect was observed on 1 large gastric ulcer after twenty-eight days of treatment, on a second after thirty-eight days and on a third after twenty-five days. The patients had all been under observation for some months and offered, therefore, an unusual opportunity for controlled study. Kirsner and Wolff concluded that sodium alkyl sulfate given hourly in large doses in conjunction with milk and cream does not produce a detectable decrease in the peptic activity of the gastric contents in human beings, that given hourly in large doses in conjunction with a diet low in fat it may decrease appreciably though temporarily the peptic activity, and that the healing of gastric ulcer is not affected by the use of very large quantities of sodium alkyl sulfate and a low fat diet.

Gill and Keele,¹⁴⁸ in studying the efficiency of milk and the various alkalis usually used in the treatment of peptic ulcer, concluded that adequate neutralization of peptic activity is obtained by raising the p_H of the gastric juice to 3.5 to 4.0 and that milk, magnesium carbonate, calcium carbonate, tribasic magnesium and calcium phosphates, colloidal aluminum hydroxide and magnesium trisilicate are the most satisfactory agents.

Upham and Chaikin,¹⁴⁹ in a clinical investigation of the aluminum phosphate gel, found that in patients with an already disturbed calcium and

phosphorus metabolism the administration of excessive amounts may produce an actual loss of phosphate. The optimum dose in the treatment of peptic ulcer is considered to be 2 tablespoons every two hours and 6 tablespoons before retiring.

Alkalosis — Zintel, Rhoads and Ravdin¹⁵⁰ found that ammonium chloride can be administered intravenously to patients with alkalosis without evident harm and that it is effective in rapidly lowering the serum carbon dioxide at the rate of approximately 1 volume per cent for each gram administered. Two per cent solutions were prepared by dissolving 20 Gm of ammonium chloride in a liter of water, 0.9 per cent sodium chloride solution or 5 per cent dextrose solution. The ammonium chloride and sodium chloride solutions could be autoclaved, but the dextrose solutions acquired a brownish color suggestive of caramelization and were not used.

Surgical Treatment — For duodenal ulcer gastric resections exceeded gastroenterostomies in number at the Mayo Clinic during 1942.¹⁵¹ About 17 per cent of the patients with duodenal ulcer and 60 per cent of those with gastric ulcer were treated surgically. DeCourcy¹⁵² reviews his experience with the ulcer problem. Stewart and Zaepfel¹⁵³ discuss the use of subtotal gastric resection in cases of bleeding and penetrating gastric ulcer and those in which malignancy cannot be definitely excluded.

Connell¹⁵⁴ reports a case of recurrent intractable duodenal ulcer treated by a partial fundusectomy on Dec 14, 1931, with no recurrence of ulcer distress up to the time of the report, July 1943. In 24 other cases with the same type of operation there were 2 postoperative deaths and 2 in which the remote result is unknown. In 19 of the remaining 20 cases the patients have been symptom free. In 1 remaining case recurrent symptoms developed in six months, a second operation disclosed an old duodenal ulcer, for which pyloroplasty was performed. The author considers the clinical results

150 Zintel, H. A., Rhoads, J. E., and Ravdin, I. S. The Use of Intravenous Ammonium Chloride in the Treatment of Alkalosis, *Surgery* **14** 728-731, 1943.

151 Walters, W., Gray, H. K., Priestley, J. T., and Counseller, V. S. Annual Report on Surgery of the Stomach and Duodenum for 1942, *Proc. Staff Meet., Mayo Clin.* **18** 505-510, 1943.

152 DeCourcy, J. L. Present Status of Gastric and Duodenal Ulcer, *Am. J. Surg.* **61** 11-15, 1944.

153 Stewart, J. D., and Zaepfel, F. M. Surgical Aspects of Gastric Ulcer, *New York State J. Med.* **44** 611-616, 1944.

154 Connell, F. G. Partial Fundusectomy (Proximal Gastrectomy). Review of Twenty-Four Cases, *Ann. Surg.* **118** 1000, 1943.

146 Kirsner, J. B., and Spitzer, E. H. Further Studies on the Effect of Sodium Alkyl Sulfate on Peptic Activity, *Gastroenterology* **2** 348-353, 1944.

147 Kirsner, J. B., and Wolff, R. A. The Effect of Sodium Alkyl Sulfate on the Peptic Activity of the Gastric Contents and on the Healing of Gastric Ulcer in Man, *Gastroenterology* **2** 93-101, 1944.

148 Gill, A. M., and Keele, C. A. Pepsin Inactivation in Ulcer Therapy, *Brit. M. J.* **2** 194-196, 1943.

149 Upham, R., and Chaikin, N. W. A Clinical Investigation of Aluminum-Phosphate Gel, *Rev. Gastroenterol.* **10** 287-297, 1943.

in the 19 cases as satisfactory, despite the return of normal gastric acidity, motility and size in the 5 other cases studied

Massive Hemorrhage—Rasberry and Miller¹⁵⁵ support the prompt feeding program for grossly bleeding peptic ulcer with adequate fluid intake to avoid shock and blood transfusions when necessary. To the 32 cases previously reported on the authors add 43, making a total of 75 personally observed and included in 2,111 cases described in the literature in which treatment consisted in some form of frequent feeding program. The gross mortality is 4 per cent and the net mortality 1.9 per cent. Surgical intervention for bleeding ulcer should be considered only when there is evidence of coincident perforation. Manzer¹⁵⁶ describes 2 cases of bleeding gastric ulcer, in 1 in a man aged 67 and in the other in a man aged 72, successfully controlled surgically and 1 fatal case in which the ulcer was not found at operation. Schiff¹⁵⁷ reports on the treatment in 160 cases of bleeding peptic ulcer with a modified Meulengracht diet. Approximately half the patients received blood transfusions. The overall mortality was 6.8 per cent and the mortality from exsanguination 3.1 per cent.

Rafsky and Weingarten¹⁵⁸ analyzed a series of 476 cases of bleeding peptic ulcer to evaluate the role of hypertension and found that the severity of the hemorrhage was little affected. The gross mortality in patients under 50 years with hypertension was increased, but this was attributed to complicating diseases not found in the patients without hypertension. In patients over 50 years of age the mortality with and without hypertension was approximately the same.

Maldonado-Allende¹⁵⁹ reports a case of rather severe hematemesis and melena of unproved origin occurring in a patient with brucellosis.

Jejunal Ulcer—Tepper and Massell,¹⁶⁰ in discussing the treatment of gastrojejunocolic fistula,

emphasize the opinion that the final procedure should include gastric resection, because anything short of this is likely to result in a therapeutic failure.

Acute Perforation—A statistically significant increase in perforated peptic ulcer was found during the period of heavy air raids in London as compared with the previous three and the following two years.¹⁶¹ The average number of perforations per month from January 1937 to August 1940 ranged from 22 to 25.5, but in months from September 1940 to May 1941 the average jumped to 35.11. In the subsequent nine months the average was 20.3, with a further decrease to 16.5 for the following periods. The statistical evidence is thus in favor of the view that some general tendency operated to cause perforations during the air raid period. Anxiety may have constituted an important cause. A significant and unexplained increase in perforations was also found in the month of December in the prewar years.

Raw¹⁶² studied a series of 312 cases of perforated gastric and duodenal ulcer with a gross mortality of 14.4 per cent. The two most important factors influencing operative mortality were the age of the patient and the interval before the operation. Supraclavicular pain was presented in 60 per cent of the cases of perforated ulcers and was of great diagnostic help.

Wakeley,¹⁶³ in a follow-up of 103 patients with perforated peptic ulcer operated on between 1924 and 1934 found that 44 per cent are still serving in the Royal Navy, only 8 per cent of these men had died, as compared with 20 per cent of a comparable series of civilians, therefore the person with perforated peptic ulcer need not be invalidated from the service.

McCabe and Mersheimer,¹⁶⁴ in studying 89 cases of acute gastroduodenal perforations found that the diagnosis was correctly made preoperatively in 89.7 per cent. In cases in which the diagnosis could not be made by the symptoms and results of physical and roentgenologic examinations the determination of the serum amylase to exclude pancreatitis and the ingestion of methylthionine chloride by stomach tube followed by peritoneal aspiration of the dye with a

155 Rasberry, E. A., Jr., and Miller, T. G. The Prompt Feeding Program for Bleeding Gastric and Duodenal Ulcer. A Report of 2,111 Collected Cases Including 75 Personally Observed, *Gastroenterology* **1** 911-921, 1943.

156 Manzer, T. T. Surgical Treatment of Massive Gastroduodenal Hemorrhage, *Northwest Med* **43** 112-113, 1944.

157 Schiff, L. The Treatment of Bleeding Peptic Ulcer with a Report of 160 Cases Treated by a Prompt Feeding Program, *South M J* **37** 535-542, 1944.

158 Rafsky, H. A., and Weingarten, M. The Effect of Hypertension on the Prognosis of Bleeding Peptic Ulcer, *Rev Gastroenterol* **11** 93-101, 1944.

159 Maldonado-Allende, I. Hemorragias digestivas en el curso de la brucelosis, *Arch argent de enferm d ap digest y de la nutrición* **18** 470-477, 1943.

160 Tepper, G. B., and Massell, T. B. Management of Gastrojejunocolic Fistula, *Am J Surg* **61** 434-438, 1944.

161 Spicer, C. C., Stewart, D. N., and Winsor, D. M. Perforated Peptic Ulcer During the Period of Heavy Air-Raids, *Lancet* **1** 14, 1944.

162 Raw, S. C. Perforation of Gastric and Duodenal Ulcers, *Lancet* **1** 12-14, 1944.

163 Wakeley, C. P. G. Late Results of Perforated Peptic Ulcer, *Lancet* **1** 11-12, 1944.

164 McCabe, E. J., and Mersheimer, W. L. Acute Gastroduodenal Perforations. Review of Metropolitan Hospital Series 1930-1941, *Am J Surg* **62** 39-49, 1943.

spinal puncture needle served as valuable diagnostic adjuncts

Williams,¹⁶⁵ in a follow-up of 100 cases of acutely perforated peptic ulcer repaired surgically, found that after an average period of three years and four months the result was considered excellent in 28 per cent, good in 27 per cent, fair in 22 per cent and poor in 23 per cent of the cases. Ashton¹⁶⁶ reports the case of a man 80 years of age in whom operation was performed for a perforated duodenal ulcer three and one-half hours after onset, with recovery. Paletta and Hill¹⁶⁷ review a series of 83 cases of patients with acute perforation of gastric or duodenal ulcer operated on between 1925 and 1942. The mortality was 16.9 per cent. The mortality in the group with gastric ulcer was twice that in the group with duodenal ulcer. Patients over 50 years of age showed a mortality six times that of patients under 50 years of age. The mortality of patients operated on after twelve hours was 25 per cent, compared with 13.6 per cent for the group operated on twelve hours or sooner after perforation. Jackson and Metheny¹⁶⁸ give a brief review of 30 cases of perforated peptic ulcer. Estes and Bennett¹⁶⁹ report 80 consecutive cases of acute perforated gastroduodenal ulcer with an operative mortality of 8.7 per cent. Reperforation occurred in 8 (12.7 per cent). Of the 53 in which end results were studied there was complete cure in only 5.6 per cent, in 71.7 per cent medical treatment was required for control of the recurrent ulcer, and in 22.8 per cent further surgical measures or hospitalization was required.

Burden,¹⁷⁰ on the basis of his personal experience, advocates gastroenterostomy in addition to closure of the acute perforation. Beitola and Martinez¹⁷¹ report on 6 perforated ulcers

treated surgically by wide gastric resection, with good results. Warren and Fallis¹⁷² report 3 cases of acute perforation of postoperative jejunal ulcer. The first of these is particularly noteworthy in that the patient first experienced a perforation of a duodenal ulcer. Eighteen months later a partial gastrectomy was performed, approximately four-fifths of the stomach being removed. About twenty months later a jejunal ulcer perforated and was repaired surgically, but it perforated again seven months later. In the second case an acute perforation of a duodenal ulcer was repaired, and a year later a posterior gastroenterostomy for pyloric stenosis was performed. A jejunal ulcer perforated almost three years later. The perforation in the third case occurred after anterior gastroenterostomy with enteroenterostomy.

Pearce,¹⁷³ in discussing the value of pain in the shoulder, obliteration of hepatic dulness and the fluoroscopic demonstration of pneumoperitoneum, advocates in the diagnosis of perforated peptic ulcer, the Trendelenburg and reversed Trendelenburg positions as valuable in demonstrating these signs.

Ulcer in Childhood—Copello¹⁷⁴ cites a number of historical references on peptic ulcer in childhood and reports an ulcer of three years' duration in a boy 14 years of age, treated by fundusectomy and without recurrence for the follow-up period of two years. Benner¹⁷⁵ reports 7 cases of duodenal and 1 of gastric ulcer found on postmortem examination in children from 2 days to 11 years of age. One case was remarkable because of the association of ulcer with possible rhubarb poisoning. Two apparently healed ulcers were found. Hutchins¹⁷⁶ reports a case of acute perforation of a duodenal ulcer in a 9 year old white girl, with recovery following operation.

Ulcer and Military Service—Edwards and Copeman,¹⁷⁷ in analyzing the cases of 356 patients complaining of dyspepsia in a military hos-

165 Williams, A. C. Perforated Peptic Ulcer. A Follow-Up Study of One Hundred Cases, *New England J Med* **230**: 785-790, 1944.

166 Ashton, G. W. A Case of Perforated Duodenal Ulcer with Recovery in a Man Aged Eighty Years, *M J Australia* **1**: 130, 1944.

167 Paletta, F. X., and Hill, W. R. Acute Perforated Gastric and Duodenal Ulcers, *Surgery* **14**: 32-37, 1943.

168 Jackson, L. E., and Metheny, D. Thirty Cases of Perforated Peptic Ulcer, *Northwest Med* **42**: 367-368, 1943.

169 Estes, W. L., Jr., and Bennett, B. A. Jr. Acute Perforation in Gastroduodenal Ulceration, with Special Reference to End-Results, *Ann Surg* **119**: 321-341, 1944.

170 Burden, V. C. Acute Perforated Ulcer, *Am J Surg* **63**: 61-68, 1944.

171 Bertola, V. J., and Martinez Carreras, A. Ulceras perforadas gastroduodenales. Gastrectomia, *Prensa med argnt* **30**: 2287-2297, 1944.

172 Warren, K. W., and Fallis, L. S. Perforation of Postoperative Jejunal Ulcers, *Surgery* **15**: 569-573, 1944.

173 Pearce, A. E. Diagnosis of Perforated Ulcer. Two Useful Maneuvers by Means of Which Pneumoperitoneum and Diaphragmatic Irritation Are Demonstrated More Clearly, *Am J Surg* **61**: 76-78, 1944.

174 Copello, O. Peptic Ulcer in Childhood, *Prensa med argnt* **30**: 2275-2280, 1943.

175 Benner, M. C. Peptic Ulcers in Infancy and Childhood. Post-Mortem Studies of Eight Cases, One Case of Possible Poisoning by Rhubarb, *J Pediat* **23**: 463-470, 1943.

176 Hutchins, L. R. Peptic Ulcer in Children. Case Report of Perforation, *Northwest Med* **43**: 40-41, 1944.

177 Edwards, H., and Copeman, W. S. C. Dyspepsia. An Investigation, *Brit M J* **2**: 640-642, 1943.

pital, found 139 with peptic ulcer, 37 with other organic disease and 180 with diagnoses of a functional disorder. The duration of freedom from pain after food was longer in the group with ulcer than in the group without. The pain was relieved by food in nearly three quarters of the patients with ulcer but in less than half of those without ulcer. Nocturnal pain was a more pronounced feature of ulcer dyspepsia than of nonulcer dyspepsia. Annis and Eldridge,¹⁷⁸ in reviewing the cases of patients admitted to an outpatient gastrointestinal clinic at a station hospital during a two-year period, found that the incidence of peptic ulcer was not greatly different than that seen in civilian practice and that the ratio of duodenal to gastric ulcer was approximately 15 to 1. Aitken¹⁷⁹ reports that 45 per cent of all the men reporting sick in an armored regiment during a two-year period were patients with dyspepsia, 45 per cent of whom were referred to hospitals for further investigation. Of these, 36 per cent were found to have gastroduodenal ulceration and 17 per cent gastroduodenitis. Tidy¹⁸⁰ considers the prevalence of dyspepsia, organic and nonorganic, in the army in the present war to be comparable to the incidence in the civilian population. Peptic ulcer began in civilian life in 81 per cent of the soldiers studied. The recurrence in the army is ascribed to unavoidable routine. Peptic ulcer caused 58 per cent of the admissions to the hospital for dyspepsia. Men with it are not suitable for army life, whereas men suffering from non-organic dyspepsia can in many cases make useful soldiers provided they are not hospitalized too long.

Kirk,¹⁸¹ in an interesting study of 50 cases of duodenal ulcer and 1 of gastric ulcer encountered at Fort Sill, makes the following comment regarding the psychosomatic aspect of the ulcer problem:

"Actually only three men developed acute and primary onset of symptoms within the 12 months preceding induction and hospitalization. In no case could a definite relationship be established with the prospect of certain military service. Wolff's^{182, 183} ulcer case histories showed pro-

longed emotional turmoil involving mainly conflict, anxiety, guilt, hostility and resentment. Every medical officer has seen a certain number of soldiers who have had all the above emotions with the possible exception of guilt, admittedly preceding the following induction in the army. On the gastrointestinal service these soldiers fitting this description very closely have in almost every instance been hospitalized for pernicious vomiting, but in no single case has a duodenal ulcer been demonstrable.

"Of the 11 soldiers developing ulcer symptoms for the first time while in service, it is easy to say that failure to obtain a promotion, transfer to less desirable posts, 'awaiting' for foreign service, constant and unemitting obedience to orders can satisfactorily establish the background of their ulcer. Actually in only a few of the psycho-neurotic personalities did these factors predominate. Outstanding was a history of onset of gastrointestinal complaints while on maneuvers eating field rations. Even overnight field problems on field rations could be relied on to produce exacerbations. Further doubt seems cast on the emotional concept of the genesis of ulcer by the inescapable fact, at least in this hospital, that patients with proven duodenal ulcer respond promptly on standard ulcer management. Complete relief of severe pain within 48 to 72 hours after being put on strict management was the rule rather than the exception. Quite the reverse occurred in the 'typical psychoneurotics'. No relief was admitted by the great majority when they were hospitalized for many weeks and either sent to duty or released from the military service on surgeon's Certificate of Disability for Discharge."

Chamberlin¹⁸⁴ attempts to standardize the diagnosis and treatment of peptic ulcer. Walters and Butt¹⁸⁵ urge further study of the value of radical surgical treatment of peptic ulcer in officers and specialists in whom ulcer develops while they are on active duty, so that more may be returned to active duty. Reports from 1,352 patients with peptic ulcer admitted to naval hospitals indicated that 92 per cent were treated medically, 55 per cent of whom were returned

178 Annis, J. W., and Eldridge, F. G. *Military Gastroenterology*, South M. J. **36** 791-798, 1943.

179 Aitken, D. G. *Dyspepsia and the Sick Parade: One Hundred and Forty-One Cases in an Armored Regiment*, J. Roy. Army M. Corps **81** 223-230, 1943.

180 Tidy, H. *Peptic Ulcer and Dyspepsia in the Army*, Brit. M. J. **2** 473-477, 1943.

181 Kirk, R. C. *Peptic Ulcer at Fort Sill*, Am. J. Digest Dis. **10** 411-413, 1943.

182 Wolf, S., and Wolff, H. G. *Evidence on the Genesis of Peptic Ulcer in Man*, J. A. M. A. **120** 670-675 (Oct. 31) 1942.

183 Mittelman, B., and Wolff, H. G. *Emotions and Gastroduodenal Function*, Psychosom. Med. **4** 5-61, 1942.

184 Chamberlin, D. T. *A Plan for Standardization of Diagnosis and Treatment of Peptic Ulcer*, Mil. Surgeon **93** 157-164, 1943.

185 Walters, W., and Butt, H. R. (a) *Management of Ulcers Among Naval Personnel*, Ann. Surg. **118** 489-498, 1943, (b) *The Treatment of Naval Personnel with Peptic Ulcer*, U. S. Nav. M. Bull. **41** 1679-1682, 1943.

to active duty, whereas 71 per cent of those treated surgically were returned to active duty. In a personal series of 35 patients 22 were treated medically, 73 per cent being returned to duty, while of 13 treated surgically 85 per cent returned to duty. Partial gastric resection was done in 85 per cent. It was noted that 25 per cent of those discharged from the navy with medical treatment had been hospitalized repeatedly. Hence radical surgical treatment is advocated for chronic recurring ulcers developing during service because the incidence of recurrence is less than the 25 per cent now found for such ulcers treated medically.

Rush¹⁸⁶ found that 53 per cent of 200 patients admitted to a large hospital in the South Pacific because of "dyspepsia" had functional disorders. The most characteristic complaint of these patients was distress induced by the taking of food. For the most part the therapeutic response was poor, leading Rush to the conclusion that such patients should be returned to the zone of the interior.

GASTRIC CANCER

Incidence—Mulsow,¹⁸⁷ studying the incidence of cancer in Iowa, found that in the city of Cedar Rapids cancer of the stomach caused 12.3 per cent of all deaths from cancer, in the cancer clinic at the Iowa State Hospital, 5.3 per cent, and in the report of the Division of Vital Statistics for the State of Iowa in 1941, 15.2 per cent of all such deaths. It is difficult to reconcile these figures with others, such as those of Cramer¹⁸⁸ and Mullen,¹⁸⁹ which ascribe 30 and 35 per cent respectively of the total cancer mortality to cancer of the stomach.

Dorn¹⁹⁰ found that in 48 per cent of the white males and 74 per cent of the white females in whom cancer develops, the growth originates in either the digestive or the genital system. Among females the genital system is attacked most frequently, while in males the most frequent localiza-

tion is in the digestive system. The incidence of cancer of the digestive tract in white males is 60 per cent higher than that in white females.

Experimental Production—Kirby¹⁹¹ and his associates in work on the experimental production of gastric cancer found that cancer did not develop in rats fed cholesterol heated to 300° C, thus refuting the theory of Roffo that cholesterol either irradiated or heated undergoes an oxidative process whereby polycyclic hydrocarbons arise which are carcinogenic for mice. In stock mice given an adequate diet with the addition of either 3,4-benzpyrene or 20-methylcholanthrene papilloma of the forestomach with a tendency to malignant evolution developed. Unlike the diffuse gastropapillomatosis associated with dietary deficiency, the papillomas induced with carcinogenic hydrocarbons tend to be localized and invasive and are not prevented or influenced by the addition of vitamin A to the diet.¹⁹² In rats receiving an adequate basal diet with the addition of either the residue of cholesterol heated to 300° C or 3,5-cholestadiene gastric tumors failed to develop.¹⁹³

Gastritis and Cancer—Alvarez¹⁹⁴ describes the case of a 55 year old man with mild abdominal discomfort and low gastric acidity for fifteen years who died of gastric cancer nineteen months after an ulcerative gastritis was found gastroscopically.

While Konjetzny¹⁹⁵ thinks that approximately 85 per cent of all gastric cancers develop on the basis of gastritic mucosal changes, Westhues,¹⁹⁶ as a result of a study of 463 resected stomachs and 40 stomachs obtained at necropsy, concludes that inflammation is not the decisive factor in the development of gastric cancer. He does not deny the possibility of cancer arising from gastritis, but he questions its frequency. Blastomatous gastric polyps are definitely precancerous,

191 Kirby, A. H. M. Attempts to Induce Stomach Tumors. I. The Effects of Cholesterol Heated to 300° C, *Cancer Research* 3: 519-525, 1943.

192 Peacock, P. R., and Kirby, A. H. M. Attempts to Induce Stomach Tumors. II. The Action of Carcinogenic Hydrocarbons on Stock Mice, *Cancer Research* 4: 88-93, 1944.

193 Kirby, A. H. M. Attempts to Induce Stomach Tumors. III. The Effects of (a) a Residue of Cholesterol Heated to 300° C, and (b) 3,5-Cholestadiene, *Cancer Research* 4: 94-97, 1944.

194 Alvarez, W. C. Cancer of the Stomach Arising in Gastritis, *Proc. Staff Meet., Mayo Clin.* 18: 225-226, 1943.

195 Konjetzny, G. E. *Der Magenkrebs*, Stuttgart, Ferdinand Enke, 1938.

196 Westhues, H. Entstehung des Magencarcinoms aus Gastritis und entzündlichen Polypen? *Arch. f. klin. Chir.* 203: 391-435, 1942.

186 Rush, A. Gastrointestinal Disturbances in the Combat Area. II. Preliminary Observations on Functional Disorders of the Digestive Tract, *J. A. M. A.* 123: 471-473 (Oct. 23) 1943.

187 Mulsow, F. W. Low Incidence of Cancer of the Stomach in Iowa, *Am. J. Digest. Dis.* 10: 297-300, 1943.

188 Cramer, W. Origin of Cancer in Man, *J. A. M. A.* 119: 309-316 (May 23) 1942.

189 Mullen, T. F. Factors Influencing the Curability of Cancer of the Stomach, *Surg., Gynec. & Obst.* 72: 297-306, 1941.

190 Dorn, H. F. Illness from Cancer in the United States. IV. Illness from Cancer of Specific Sites Classed in Broad Groups, V. Illness from Cancer of Individual Specific Sites, *Pub. Health Rep.* 59: 33 and 65, 1944.

but they are not inflammatory, hence cancers developing in them are not a result of inflammation

Guiss and Stewart,¹⁹⁷ after a careful review of the literature and a detailed histologic study of stomachs obtained from persons of all ages from birth to senility with and without gastric or extragastric cancer arrive at important conclusions

"Intestinal metaplasia, pyloric gland heterotopia, mucosal cyst instances of dedifferentiation of specialized cells and lymphoid collections are not present at birth and must therefore develop postnatally, probably as a result of mucosal damage. Intestinal metaplasia, heterotopia of the pyloric glands, mucosal cysts, heavy leukocytic infiltration and large numbers of lymphoid aggregates are never found in truly normal stomachs but are all evidences of gastritis changes. Stomachs of patients who died of cancer other than gastric cancer are essentially identical with those who died from other causes, except that they contain fewer lymphoid follicles and collections, and less leukocytic infiltrate. This difference is directly proportional to the degree of malnutrition present and not due to the presence of cancer itself in the patient. Eighty-two per cent of stomachs from apparently normal persons who died within the gastric cancer age (over 40) show microscopic evidence of chronic atrophic gastritis. Ninety-seven per cent of stomachs with gastric carcinoma show associated chronic atrophic gastritis. There is a similar incidence of chronic atrophic gastritis in association with gastric diseases other than carcinoma. The chronic atrophic gastritis associated with gastric carcinoma is a non-specific 'reaction' to inflammation and gastric injury in general, and there is no evidence to suggest an etiologic relationship other than that chronic atrophic gastritis may be caused or intensified by the presence of carcinoma in the stomach.

"The factors included in the present concept of chronic atrophic gastritis, i. e. mucosal atrophy, increased amounts of leukocytic infiltrate and lymphoid aggregates, intestinal metaplasia and pyloric gland heterotopia are all rather closely correlated, variation in one factor tending to be associated with proportionate changes in the others. This correlation probably justifies the consideration of these changes as a pathologic entity.

"The often reiterated claim that chronic atrophic gastritis is a precancerous lesion re-

ceives no positive support as a result of this study. The slight difference in incidence of gastric atrophy between cancerous and noncancerous stomachs is far from being convincing. Atrophic gastritis is an exceedingly common condition with advancing age. Mere statistical correlation of incidence of gastric atrophy and of gastric cancer is quite insufficient to show causal relation. Both atrophy and cancer appear to be events in aging organs. Were the effort made, it would doubtless be easy to show that gastric cancer was correlated not only with gastric atrophy but likewise with atrophy of other organs even in fact with atrophy of such anatomically unrelated structures as the genitalia, breasts, circulatory apparatus or even skin, thus reducing to absurdity the conclusions based on mere statistics as to incidence.

"To assert on morphologic grounds that the origin of gastric cancer depends on the existence of gastric atrophy would require far more evidence. It would at least require proof that early gastric cancer begins in, and can be directly traced to, an area of atrophy to the exclusion of other areas. From the very nature of gastric material universally available in large clinics, this type of evidence, although it may eventually appear, will be long in coming. Could even this be proved correct, the larger question would still remain unanswered as to why A, with gastric atrophy, gets cancer and B, with the same atrophy, does not. Prematurity in formulating important conclusions in matters of this sort is unjustified."

On the other hand, Warren and Meissner¹⁹⁸ point out that the histologic changes in chronic gastritis should be divided into exudative and epithelial, the former have no direct significance as a precancerous lesion, but the latter when severe may be comparable to well recognized premalignant lesions elsewhere in the body. Hence these authors assume that some gastric cancers arise on this basis, even though conclusive statistical proof is not available.

Prognosis and Classification—Dochat and Gray¹⁹⁹ studied the cases of 1,251 patients with gastric carcinoma operated on at the Mayo Clinic between the years 1922 and 1934. The tumors were classified into four types based on the extent of the lesion: type A, those in which the carcinoma involves only the mucosa and is not seen

197 Guiss, L. W., and Stewart, F. W. Chronic Atrophic Gastritis and Cancer of the Stomach, *Arch Surg* 46 823-843 (June) 1943

198 Warren, S., and Meissner, W. A. Chronic Gastritis and Carcinoma of the Stomach, *Gastroenterology* 3 251-256, 1944

199 Dochat, G. R., and Gray, H. K. Carcinoma of the Stomach. Prognosis Based on a Combination of Duke's and Broders' Method of Grading, *Am J Clin Path* 13 441-449, 1943

microscopically below the muscularis mucosae, type B₁ lesions are those in which the carcinoma extends from the submucosa into the muscularis and involves all or part of the gastric musculature, type B₂ lesions have spread through the entire wall and involved the serosa, type C lesions include those in which there is metastatic involvement of the regional lymph nodes. The survival rate graded in this manner was compared with the survival rate graded by the method of Biodeis. It was found that the grade of the lesion and the extent of its spread taken together give a better index of the duration of postoperative life than does one of these methods alone.

Puderbach and Ficarra²⁰⁰ report a gastric tumor described histologically as a "malignant carcinoid" although the silver stains were unsatisfactory. From a practical viewpoint the differentiation is not too important, except that carcinoids and indeed certain adenocarcinomas are generally very slow in growth and metastasis.

Wood,²⁰¹ in an interesting discussion of adenocarcinoma of the pyloric end of the stomach, presents 2 cases with metastases in the lymph node containing squamous cells as well as glandular components and reviews 19 cases reported in the literature. In discussing the mechanism of their development, Wood reviews the experimental studies of Stewart and Lorenz and other workers and concludes that "direct neoplastic stimulation of undifferentiated basal cells in the gastric mucosa is the essential factor in the histogenesis of squamous cell tumors of the pyloric region of the stomach."

Natural History—Palmer,²⁰² commenting on the meagerness of knowledge of the natural history of gastric carcinoma, emphasizes the greatest variations in the rate of growth and extension. The extremes are represented by the "acute" growths, such as the rapidly metastasizing tumors described by Jaicho, and the very "chronic lesions" such as that described by Eusterman and Balfour in which the patient was operated on nine and one-half years after the onset of symptoms, two and one-half years after a diagnosis of gastric carcinoma was made, and yet a resectable lesion was found. The patient

was still alive and well nine years later. Palmer describes another case with fairly good evidence of gastric cancer for eleven years. In a third instance a lesion identified roentgenologically and gastroscopically as a small ulcerating carcinoma was observed for four years with 16 roentgenologic examinations and 22 gastroscopic examinations before resection was carried out. Symptoms were minimal and there was no loss of weight. The resected lesion was a small ulcerated mucinous carcinoma without evidence of metastasis. The factors determining or influencing these various rates of growth are unknown, although in general the biologic behavior of the tumor corresponds roughly with the degree of cellular differentiation in terms of Biodeis's grading. The therapeutic implication is that as a rule gastric carcinoma should be resected unless there exist proved distant metastases. There is very little evidence to support the view that the removal of the primary tumor exerts a favorable influence on the growth of secondary lesions.

Feldman²⁰³ reports 3 instructive cases of long-standing carcinoma of the stomach. In the first, that of a 56 year old man with slight dyspeptic symptoms of two years' duration, a roentgenogram of the stomach disclosed a seemingly insignificant prepyloric narrowing. In 5 further roentgen ray examinations during seventeen years, progressive narrowing was noted. At operation an inoperable carcinoma was found. In the second case, a 59 year old man gave a history of digestive complaint extended over a period of three years. The roentgen ray examination at the time of the first symptoms revealed a slight and seemingly insignificant narrowing of the prepylorus. Two years later with a recurrence of symptoms, roentgenologic examination again revealed a "spastic pylorus and narrowing of the prepylorus thought to be due to a gastritis." One year later "roentgen studies revealed a partial pyloric obstruction with an annular infiltrating ulcerating carcinoma. At operation an inoperable carcinoma was found." In the third case, a man 73 years old when admitted to the hospital was followed during six years. Four sets of roentgenograms in this period showed the progressive narrowing of the pylorus, caused as proved at operation, by an inoperable carcinoma. The 3 cases are well documented with roentgenograms and constitute further convincing evidence of the chronicity of certain gastric carcinomas.

200 Puderbach, W. J., and Ficarra, B. J. Malignant Carcinoid of the Stomach. Case Report of a Patient Treated by Subtotal Gastrectomy, *Am J Surg* 61:121-123, 1943.

201 Wood, D. A. Adenoacanthoma of the Pyloric End of the Stomach, *Arch Path* 36:177-189 (Aug) 1943.

202 Palmer, W. L. The Duration of Gastric Cancer, *Gastroenterology* 1:723-736, 1943.

203 Feldman, M. The Life Cycle of Carcinoma of the Stomach, *Gastroenterology* 2:60-64, 1944.

Alvarez²⁰⁴ reports the case of a man with an old duodenal ulcer who was found at operation to have a leather bottle type of stomach with a malignant ulcer which was excised near the cardia. Two years later another such ulcer was found.

Fergusson²⁰⁵ reports on a 39 year old patient with carcinoma of the stomach invading the right ureter and producing a urinary extravasation on the right side as the result of the obstruction of the ureter.

Diagnosis—Wasch and Epstein²⁰⁶ call attention to the double contrast method of detecting carcinoma of the cardia roentgenologically. The tumor mass may be clearly demonstrated in the air bubble with the stomach empty or only partially filled with barium sulfate solution. Better contrast roentgenograms were obtained by inflating the stomach with air through a Levine tube.

Jenkinson and Lattaier²⁰⁷ report 2 instructive cases in which spasm of the antrum produced the roentgenologic criteria of gastric carcinoma. An interesting case is described of gastric carcinoma not diagnosed by gastroscopic or roentgenologic examination but nevertheless found at operation to be present and invading both the pancreas and the spleen²⁰⁸.

A most interesting experiment²⁰⁹ in the early diagnosis of gastric carcinoma consists in the mass roentgenologic study of 2,413 men and women over the age of 50 who had no digestive symptoms of appreciated significance. Of these, 491 were reexamined a year or more later. Three were found to have unsuspected malignant gastric tumors, 2 of them having a carcinoma and 1 a lymphosarcoma. All 3 underwent subtotal gastric resection. The lymphosarcoma was not found by the surgeon at operation but was found on reoperation several months later. One of the two carcinomas situated near the pylorus

presented an ulcerated area less than 1 cm in diameter. It had entered the muscularis at only one area and had not metastasized. The method of study was a rapid fluoroscopic examination of the stomach in an effort to differentiate between the abnormal and the normal. In the cases in which the stomach did not appear normal, a subsequent, more detailed, examination was made. The chief difficulty encountered was not the speed of the examination itself but the handling of the patients, guiding them back and forth from the dressing rooms, keeping them moving steadily into the fluoroscopic room, etc. Two assistants and a stenographer were required to keep the examiner busy. The cost of examination was approximately 48 cents per person, this did not include a charge for the service of the roentgenologist or overhead charges for the equipment, but merely the actual cost of secretarial and technical help, stationery, films, etc. An interesting by-product was the relatively large number of abnormalities other than carcinoma disclosed, such as 54 instances of deformity of the duodenal bulb with or without crater, 7 of cardiospasm and 25 of diaphragmatic hernia. Whether or not these results warrant for the mass of the populace routine roentgenologic examination of the stomach at intervals is questionable, but they certainly emphasize the importance of roentgenologic examination, the need for an examination at the slightest indication and the low cost with which such examinations can be made on a quantity basis.

Thorstad²¹⁰ reviews 970 cases of malignant gastric neoplasms observed from 1928 to 1942 in a private and in a charity hospital. Of the patients observed in the private hospital 42.3 per cent were clinically inoperable, as compared with 76.6 per cent in the charity hospital. Gastrectomy was performed on 19.4 per cent of the patients at the private hospital and in 9.8 per cent of those at the charity hospital. No evidence was found to indicate a significant improvement in either the diagnosis or the treatment of early carcinoma of the stomach during this fifteen year period.

Bolen²¹¹ describes a pattern in the dried red blood cell which not only is a "sensitive indicator" of the presence of carcinoma but 'can be used at intervals to determine the course of the disease, presence of metastases, and end results after surgery, deep x-ray therapy, or radium implantation'. The evidence offered is not convincing to the reviewers.

204 Alvarez, W. C. Benign Appearing Ulcers Coming Repeatedly in a Leather Bottle Stomach. Report of Case, Proc. Staff Meet., Mayo Clin. **18** 298-299, 1943.

205 Fergusson, J. D. Ureteral Stricture with Perinephric Urinary Extravasation Caused by Metastases from a Silent Carcinoma of the Stomach, Brit. J. Surg. **31** 283-286, 1944.

206 Wasch, M. G., and Epstein, B. S. The Roentgen Visualization of Tumor of the Cardia, Am. J. Roentgenol. **51** 564-571, 1944.

207 Jenkinson, E. L., and Lattaier, K. K. Non-Organic Gastric Filling Defects Simulating Carcinoma, Radiology **41** 444-450, 1943.

208 Case Records of the Massachusetts General Hospital, Cabot Case 30092, New England J. Med. **230** 264-266, 1944.

209 St. John, F. B., Swenson, P. C., and Harvey, H. D. An Experiment in the Early Diagnosis of Gastric Carcinoma, Ann. Surg. **119** 225-231, 1944.

210 Thorstad, M. J. The Outlook on Carcinoma of the Stomach, Am. J. Surg. **64** 242-247, 1944.

211 Bolen, H. L. Diagnostic Value of Blood Studies in Malignancy of the Gastrointestinal Tract, Am. J. Surg. **63** 316-323, 1944.

Surgical Treatment—In 127 malignant tumors observed by Amesti²¹² between 1938 and 1942 the resectability rate was 55.76 per cent with a mortality of 26 per cent. Metheny²¹³ concludes that at least 50 per cent should be subjected to operation, and the surgeon must be willing to accept a high mortality rate. When 50 per cent of 42 tumors were operated on, 12 resections were done, with a mortality of 50 per cent and a chance of cure of 14.5 per cent. When 30 per cent of 67 malignant tumors were operated on, 10 per cent were resected, with a 25 per cent mortality and a 7.5 per cent chance of cure. When only 10 per cent of 34 tumors were operated on, 8 per cent were resected, with no mortality and a 10 per cent chance of cure.

Morris²¹⁴ reviews the history of surgical treatment of gastric carcinoma from the time of Billroth to the present day, notes that at Bellevue Hospital there have been three times as many admissions for gastric carcinoma as for gastric ulcer and estimates that the incidence of resectable carcinoma in the United States is about 10,000 per year, and yet only 3,000 resections have been reported in this country. The American College of Surgeons has 1,279 registered five year cures. Twenty per cent of the patients dying from carcinoma of the stomach show no distant metastases at autopsy. In the last twenty years at the Charity Hospital in New Orleans, the resectability rate has more than doubled while the operative mortality has been cut to one third of that ten years ago. Morris estimates that 50 per cent of the patients seen in the hospitals have cancers which are inoperable, that only 25 per cent have resectable cancer and that 20 per cent of those with resected tumors may be expected to survive for more than five years.

These estimates reflect the present status, but there is much reason to hope that in the years to come the number of resectable carcinomas will greatly exceed the present figure of 25 per cent, that the five year cures will likewise increase and that the mortality rate will decrease. Thus Walters and his associates²¹⁵ report that resection was carried out on 40 per cent of the patients operated on for malignant disease in the

year 1942, with a mortality rate of 67 per cent, the lowest in the records of the Mayo Clinic.

Allen²¹⁶ reports that 14 per cent of 255 gastric ulcers thought to be benign proved to be malignant microscopically. Healing of the ulcer under adequate medical management did not assure the absence of malignancy. When operation was done with a clinical diagnosis of cancer, the five year cure rate was 20 per cent, whereas when operation was undertaken with a diagnosis of ulcer and cancer found, the cure rate increased to 40 per cent. The five year cure rate including mortality as reviewed in 1933 and 1939 has not been appreciably improved, but an increased number of patients have had more months of respite from symptoms.

Lahey and Marshall²¹⁷ describe 73 patients who underwent total gastrectomy at the Lahey Clinic, with a mortality of 33 per cent, in the last two years in 28 operations the mortality was reduced to 18 per cent. Most postoperative deaths were due to intra-abdominal infection. Microscopic examination of the lymph nodes disclosed metastatic involvement in 87 per cent of the cases with resection. Of the 48 patients surviving gastrectomy, 15 lived more than a year and 7 have lived two or more years. One patient is alive and well after four and one-half years, and another is well after six years. These figures for survival are to be contrasted with the average life expectancy of five months for patients with such tumors when no resection is carried out. Clagett and Root²¹⁸ report an adenocarcinoma of the cardia in a young woman 21 years of age successfully treated by transthoracic resection. Eight such operations were performed, with 1 postoperative death. Sweet²¹⁹ reports 7 similar cases.

Because of the bacteriologic flora found in the stomachs of patients with gastric carcinoma, the use of 5 to 10 Gm of sulfathiazole preoperatively is advised.²²⁰

212 de Amesti, F. Malignant Tumors of the Stomach, *Am J Surg* **63** 78-85, 1944.

213 Metheny, D. Curability of Gastric Carcinoma, *Northwest Med* **42** 17-18, 1943.

214 Morris, H. J. End Results in Surgical Treatment of Gastric Carcinoma, *New Orleans M & S J* **96** 254-262, 1943.

215 Walters, W., Gray, H. K., Priestley, J. T., and Counseller, V. S. Annual Report on Surgery of the Stomach and Duodenum for 1942, *Proc Staff Meet, Mayo Clin* **18** 505-511, 1943.

216 Allen, A. W. Benign and Malignant Ulcers of the Stomach, *Bull New York Acad Med* **20** 15-24, 1944.

217 Lahey, F. H., and Marshall, S. F. Indications for an Experience with Total Gastrectomy Based upon Seventy-Three Cases of Total Gastrectomy, *Ann Surg* **119** 300-320, 1944.

218 Clagett, O. T., and Root, G. T. Transthoracic Resection of the Cardia of the Stomach, *Proc Staff Meet, Mayo Clin* **19** 187-191, 1944.

219 Sweet, R. H. Total Gastrectomy by the Transthoracic Approach. Report of Seven Cases, *Ann Surg* **118** 816-837, 1943.

220 Priestley, J. T., Thompson, L., and Sealy, W. B. Bacteriologic Aspects of Gastric Contents in Presence of Surgical Lesions of the Stomach and Duodenum, *Proc Staff Meet, Mayo Clin* **19** 1-4, 1944.

A defective diet and chronic loss of blood are not considered sufficient to explain the hypoproteinemia and anemia²²¹ Patients who have had total gastrectomy for cancer have an impaired ability either to digest or to absorb fat in the diet²²² The blood lost during various gastrointestinal operations is not excessive when compared with that lost during other types of operations²²³ The intravenous administration of aminoacetic acid, with or without the simultaneous ingestion of choline, failed to increase the urinary output of creatine or creatinine²²⁴ The failure is attributed to coexisting hepatic insufficiency Elman,²²⁵ in discussing the parenteral administration of fluids and food, stresses the value of intravenous administration of amino acid (in the form of a hydrolyzate of casein) to prevent or correct protein loss when assimilation from the gastrointestinal tract is impossible In complete starvation 100 Gm of protein are lost daily Elman estimates that 100 Gm of dextrose is sufficient to reduce the protein loss two thirds and recommends as a basic formula the daily administration of 100 Gm of dextrose and 50 Gm of amino acids, to which addition dextrose protein, saline solution, vitamins and fluids may be added as indicated

Benign Tumors—Weinberg and Raider²²⁶ discuss pedunculated tumors of the stomach and report a case in which the filling defect caused by the polyp was observed to vary between the stomach and the duodenum on different roentgenologic examinations Centeno²²⁷ found that

221 Ariel, I, Rekers, P E, Pack, G T, and Rhoads, C P Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract, *Ann Surg* **118** 366-371, 1943

222 Rekers, P E, Pack, G T, and Rhoads, C P Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract VI Disorders in Alimentary Digestion with Absorption in Patients Who Have Undergone Total Gastrectomy for Carcinoma of the Stomach, *Surgery* **14** 197-215, 1943

223 Oppenheim, A, Pack, G T, Abels, J C, and Rhoads, C P Estimation and Significance of Blood Loss During Gastrointestinal Surgery, *Ann Surg* **119** 865-872, 1944

224 Abels, J C, Kupel, C W, Pack, G T, and Rhoads, C P Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract XIII The Effect of Glycine on the Urinary Excretion of Creatine and Creatinine, Especially by Patients with Cancer of the Gastrointestinal Tract, *Cancer Research* **4** 145-149, 1944

225 Elman, R Parenteral Fluids and Food in Gastrointestinal Disease, *Bull New York Acad Med* **20** 220-236, 1944

226 Weinberg, T B, and Raider, L Pedunculated Tumors of the Stomach Prolapsing Through the Pylorus, *Radiology* **41** 52-55, 1943

227 Centeno, A M Tumores benignos del estómago, *Prensa med argent* **30** 2196-2206, 1943

29 benign tumors of the stomach had been observed in Argentina between 1925 and 1942

Lymphosarcoma—McSwain and Beal²²⁸ found that lymphosarcoma constitutes 19 per cent of the malignant lesions of the gastrointestinal tract The differentiation from carcinoma was seldom made before histologic examination Two suggestive diagnostic points on roentgenologic examination were the large size of the lesion in relation to the short duration of symptoms and the presence of whorl-like defects in the barium outline Of 20 patients, 6 were alive without evidence of recurrence after surgical removal and 2 after roentgen therapy The mortality was 42 per cent The prognosis was most favorable for those for whom complete removal was possible Roentgen therapy is advised in every case unless the lesion has been completely eradicated In a series of 258 patients with initial diagnoses of gastric neoplasm Yarnis and Colp²²⁹ found the correct final diagnosis for 8 (3.2 per cent) to be lymphosarcoma, seven of the lesions being typical small round cell tumors and one a reticulum cell sarcoma The clinical picture was indistinguishable from that of carcinoma The roentgenologic examination disclosed exaggerated folds and giant rugae Gastroscoopically the exaggerated rugae with ridgelike elevations and nodular or polypoid tumors were covered with relatively normal mucosa with very minimal ulceration The authors question whether diffusely infiltrating nonulcerative lymphosarcoma is a surgical disease, for better results may be obtained by radiation therapy alone The prognosis, however, is poor, for other authors have been able to collect only 26 five year cures in the entire literature of some 246 cases Bassler²³⁰ reports 4 cases of leiomyosarcoma An enormous ulcer of the lesser curvature of the stomach,²³¹ found to be lymphosarcomatous when resected, is described A 27 year old soldier was found to have a round cell sarcoma of the stomach²³² A malignant lymphoblastic lymphoma of the stomach with

228 McSwain, B, and Beal, J M Lymphosarcoma of the Gastro-Intestinal Tract Report of Twenty Cases, *Ann Surg* **119** 108-123, 1944

229 Yarnis, H, and Colp, R Lymphosarcoma of the Stomach, *Gastroenterology* **1** 1022-1039, 1943

230 Bassler, A Leiomyosarcoma of the Stomach Presenting Four Cases, *Am J Digest Dis* **10** 342-344, 1943

231 Ayerza, L, Chavarri, M A, and Lellis, J T M Nicho gigante del estomago por linfosarcoma, *Arch argent de enferm d ap digest y de la nutrición* **19** 197-201, 1944

232 Porritt, A E, Hughes, K E A, and Campbell, R J C Sarcoma of the Stomach, *Brit J Surg* **31** 395-398, 1944

extension to the transverse colon and involvement of regional lymph nodes was encountered in a patient with a benign giant cell tumor of the left femur.²³³ Doran and Doran²³⁴ report a lymphosarcoma of the stomach with perforation into the gastocolic omentum. Resection was followed by recovery.

Hodgkin's Disease—Jungman²³⁵ reports an unusual case of Hodgkin's disease of the stomach occurring in a 60 year old man who had experienced epigastric discomfort one hour before meals, relieved by food, for two months. Severe pain about the umbilicus followed the meal

233 Case Records of the Massachusetts General Hospital, Cabot Case 30072, New England J Med **230** 201-204, 1944

234 Doran, W T, and Doran, W T, Jr. Lymphosarcoma of the Stomach with Perforation. Gastric Resection with Recovery, Am J Surg **61** 136-137, 1944

235 Jungman, H. Hodgkin's Disease of the Stomach, Brit J Radiol **16** 386-387, 1942

Roentgenologic examination of the stomach showed severe hypertrophic gastritis with rigid folds extending from the cardia to the pylorus. Peristalsis was very sluggish and almost invisible at the middle part of the lesser curvature. The gastrosopic appearance suggested a widely infiltrated carcinoma. The pathologic report was Hodgkin's lymphogranuloma infiltrating all the coats of the stomach. Lahey²³⁶ describes the most extensive operation ever undertaken in his experience, namely total gastrectomy, splenectomy, omentectomy, colectomy and resection of the left lobe of the liver. The operation was technically successful, although the patient died five months later from a recurrence diagnosed by the pathologists as Hodgkin's disease.

(10 Bc Concluded)

236 Lahey, F H. Total Gastrectomy, Splenectomy, Resection of the Left Lobe of the Liver, Omentectomy and Colectomy upon One Patient in One Operation, Ann Surg **119** 222-224, 1944

BRAIN ABSCESS ASSOCIATED WITH CONGENITAL HEART DISEASE

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Brain abscess is a relatively unrecognized complication of congenital heart disease, so little known that only rarely does one find reference to it in any standard textbook of medicine. This obscurity must result in part at least from the scarcity of published cases, only 23 having been reported to date. Hanna¹ in 1941 collected 17 cases from the literature and added 6 more of his own. Of this entire series, in only 3 cases, 1 reported by Ingham² and 2 reported by Wechsler and Kaplan,³ was the disease correctly diagnosed prior to death and surgical drainage of the abscess attempted. In all probability, this apparent obscurity and paucity of reported cases represent the failure either of their recognition or of their publication rather than the rarity of their occurrence.

Three cases of brain abscess associated with septal defects of the heart coming to autopsy at the Mallory Institute of Pathology of the Boston City Hospital during the years 1936 to 1943 form the body of this paper. These cases were selected from the 7,880 autopsies performed during these years, which included 53 cases of congenital heart disease of all types. There were no other instances of encephalomalacia encountered in the latter group—a point of some interest in relation to the discussion which follows.

REPORT OF CASES

CASE 1—A 10 year old girl was admitted to the Boston City Hospital with a history of listlessness and extreme lethargy for seven days. A persistent cough appeared three to four days later, followed by intractable vomiting. She became increasingly drowsy up to the day of her admission to the hospital, on which day she complained of a severe headache with pain in

the left ear. There were no signs of fever, stiff neck or localizing neurologic symptoms up to the time of her admission. Her past history revealed that from birth she had been recognized as having congenital heart disease and had always been restricted to a regimen of limited activity. No history of cyanosis could be elicited. Of some passing interest is the fact that the patient was a 3½ pound (1,560 Gm) premature infant at birth.

Physical Examination—On admission she appeared to be a well developed, dehydrated, restless child having intermittent, spastic, purposeless movements of the arms. Soon after admission she became disoriented and lapsed into coma. Her temperature was 103 F, pulse rate 120 and respiratory rate 26. Cyanosis was moderate but definite. There was a well defined clubbing of the fingers. The heart was not enlarged. The pulse rate was extremely rapid. A machinery murmur, most noticeable in the apical region, was heard over the entire precordium. Nuchal rigidity and positive Kernig and Brudzinski reflexes were prominent. There were no other neurologic signs.

Laboratory Studies—There was time for only a lumbar puncture, which gave the following results. The fluid was purulent, with 34,000 cells per cubic millimeter, mostly polymorphonuclear leukocytes, and the sugar was diminished. Smear of the spinal fluid demonstrated many gram-positive cocci in pairs and short clusters. Culture of the spinal fluid revealed a streptococcus with alpha hemolysis. Culture of the blood at this time showed no growth.

Course—Treatment was started with 2.5 Gm of sulfadiazine, intravenously injected, and fluids administered parenterally, but the coma deepened, the temperature rose to 104 F, breathing became gasping, and the patient died with a terminal convulsion seven hours after her admission.

Postmortem Examination—The only significant observations pertained to the heart and brain. The heart weighed 150 Gm (approximately the usual size and weight) and presented the classic tetralogy of Fallot, with (a) dextroposition of the aorta, (b) pulmonary stenosis, with a valvular lumen 0.3 cm in diameter, (c) cor pulmonale, the right ventricle measuring 1.2 cm in thickness as compared with the thickness of the left ventricle of 1 cm and (d) an oval defect 1 by 1.2 cm, lying in the tendinous portion of the interventricular septum. The brain weighed 1,300 Gm (slightly increased in size and weight). The surfaces were flattened, with increased vascularity of the leptomeninges and narrowing of the sulci. There was a definite edema of the left cerebral hemisphere, with widening of this hemisphere. The base of the brain was covered with a layer of yellow-white purulent exudate. In the left parieto-occipital lobe there was

From the Mallory Institute of Pathology of the Boston City Hospital.

1 Hanna, R. Cerebral Abscess and Paradoxical Embolism Associated with Congenital Heart Disease. Report of Seven Cases with Review of Literature, *Am J Dis Child* 62:555 (Sept) 1941.

2 Ingham, D. W. Paradoxical Embolism, *Am J M Sc* 196:201 (Aug) 1938.

3 Wechsler, I. S., and Kaplan, A. Cerebral Abscess (Paradoxical) Accompanying Congenital Heart Disease, *Arch Int Med* 66:1282 (Dec) 1940.

an abscess cavity, thin walled, up to 2 cm in diameter occupying chiefly the central and convoluted white matter. At one point the abscess had extended to within 0.2 cm of the pia, and at another point it had ruptured into the posterior horn of the left lateral ventricle, producing a ventricular empyema and meningitis.

Microscopically, the abscess cavity was filled with purulent exudate containing many demonstrable cocci. The abscess wall was thin and poorly formed, showing active proliferation of fibroblasts. No thrombosed arteries or veins were demonstrable, nor were there any other lesions in the brain suggestive of infarcts or hemorrhages.

The remainder of the observations made at autopsy were not pertinent to the present discussion save for the fact that no foci of infection were found anywhere else in the body, including extremities, lungs, middle ears and sinuses.

Bacteriologic Studies—There was no growth in the cultures of the heart blood or the lungs. The culture of the brain abscess grew streptococci with alpha hemolysis, fusiform bacilli and *Borrelia vincenti*. The culture of the spinal fluid grew streptococci with alpha hemolysis.

Comment—This case is typical of the disease complex in one of its more confusing manifestations—a brain abscess containing, besides streptococci with alpha hemolysis, obvious oral organisms, namely, fusiform bacilli and spirochetes. No path of extension from the oral cavity to the brain or recognizable origin for infected emboli could be found.

CASE 2—A 19 year old married Negro woman entered the hospital on Aug 28, 1936 for the fourth time.

In 1926, at 9 years of age, she injured her right hip by a fall and was subsequently hospitalized for drainage of the hip joint. An uneventful recovery followed, with no further symptoms referable to this infection.

Approximately three to four years later in a routine examination her mother was found to have a positive Wassermann reaction, and the patient was likewise found to have a positive reaction. She received regular and adequate antisyphilitic treatment until she was discharged as cured.

In 1934 she again entered the hospital, because of failing vision. A diagnosis of bilateral cataracts was made, and at the same time the patient was found to be diabetic. The diabetes was controlled by diet and insulin.

Her fourth, and final, admission was initiated by an incidental acute glossitis. At this time she admitted that she had stopped taking insulin several months before reentering the hospital.

In the course of the physical examination at the time of her admission, intense cyanosis of the mucous membranes with clubbing of the finger tips and toes was noted. Questioning revealed that the patient had noted these changes since childhood, but she disclaimed any knowledge of heart disease or any symptoms referable to cardiac decompensation.

Physical Examination—She was an alert, well oriented, cooperative Negro woman with the obvious cyanosis and clubbing of finger tips and toes already mentioned. The margins of the gums were retracted, and the tongue was edematous and covered with irregular patches of exudate. The heart was not enlarged. The pulse rate was 120 with regular rhythm, and a continuous machinery murmur was heard best over

the second left interspace. The abdomen was normal. Deep tendon reflexes of the lower extremities were absent, but sensation, pain and vibratory sense were within normal limits.

Laboratory Studies—The only important results of laboratory tests were a hemoglobin content of 122 to 128 per cent, a red blood cell count of 7,000,000 cells per cubic millimeter and a white blood cell count of 5,100 cells per cubic millimeter. The blood sugar was 308 mg per hundred cubic centimeters, and the urine was essentially normal save for a 4 plus reduction of sugar with traces of acetone. Culture of material from the mouth demonstrated pneumococci, *Streptococcus viridans*, *Micrococcus catarrhalis* and *Staphylococcus aureus*.

Course—With a diet supplemented by 40 units of regular insulin daily the hyperglycemia and glycosuria were gradually controlled. The patient was well and ambulatory by the fifth day in the hospital but was asked to remain in order that her diabetes might be more carefully controlled. On the fifteenth day, after she had received 50 units of insulin, clonic convulsive movements of the left arm suddenly developed. Since it was assumed that the neurologic seizure was a reaction to the insulin, the dose was lowered to 40 units the next day but was again followed by a similar incident, with a residual weakness of her left arm and leg and a slight weakness of the left facial muscles. On the following day, the hemiplegia was well defined. Lumbar puncture at this time yielded a slightly cloudy fluid under no elevation in pressure, having 250 white blood cells per cubic millimeter, 92 per cent of which were polymorphonuclear leukocytes. Twenty-four hours later there was noticeable stiffness of the neck. The spinal fluid was now grossly cloudy, containing 3,000 white blood cells per cubic millimeter with 87 per cent polymorphonuclear leukocytes. On the next day, the third since the onset of signs referable to the central nervous system, the patient was in deep coma with obvious fulminating meningitis and hemiplegia of the left side. Culture of the cerebrospinal fluid now revealed an atypical streptococcus with alpha to gamma hemolysis. Cultures of the blood repeatedly showed no growth. The rapidly progressive course of the disease could not be altered by any therapy, and she died nineteen days after her admission and four days following the onset of the signs and symptoms referable to the central nervous system.

Postmortem Examination—The only observations of significance were in the mouth, heart and brain. The gums were soft, necrotic and spongy, showing areas of frank exudation. The heart weighed 280 Gm and was slightly increased in weight but extremely increased in size. There were multiple congenital defects present which constituted the tetralogy of Fallot, together with a patent ductus arteriosus. The right ventricle measured 1.8 cm in thickness, in contrast to the thickness (1.5 cm) of the left ventricle. In the interventricular septum there was found a circular defect, 2 cm in diameter, lying just below the aortic valve ring. The pulmonary valve orifice was completely occluded by a membranous septum. The ductus arteriosus was widely patent, with a diameter of 1.5 cm. The aorta was dextroposed and was so situated as to receive blood from both the right and the left ventricle.

The brain weighed 1,080 Gm, was decreased in size and weight and showed evidence of considerable cerebral edema as demonstrated by the flattening of convolutions and obliteration of the sulci. The subarachnoid space contained yellow-green purulent exu-

date, distributed most heavily over the left cerebral hemisphere and base of the brain. Within the right parieto-occipital lobe there was a roughly spherical cavity, 4 cm in diameter, filled with thick purulent exudate, communicating with the lateral ventricle (fig 1).

The remaining organs were essentially normal save for slight bilateral bronchopneumonia of the lower lobes of the lungs.

Microscopically, sections of the right hemisphere evidenced a fairly recent brain abscess, showing slight fibrosis of the wall. The meninges contained a sparse infiltration of lymphocytes and polymorphonuclear leukocytes. No organisms were seen in the tissue sections of the brain abscess and meninges. The gross diagnosis of bronchopneumonia was confirmed by characteristic microscopic appearance of focal areas of infiltration with polymorphonuclear leukocytes about widely scattered bronchioles.

Bacteriologic culture of the meninges showed no growth, perhaps because of the sulfonamide medication.

Comment—This case presented an unusual opportunity for following the course of the disease from its very inception. The patient was in the hospital for incidental reasons when localizing neurologic signs sud-



Fig 1—The abscess is represented by the irregularly shaped cavity just above and communicating with the posterior horn of the lateral ventricle. The central white matter above and lateral to the cavity is softened and hemorrhagic. The apparent enlargement of the right parietal lobe is due to cerebral edema.

denly developed. The suddenness and the dramatic character of the onset led clinical observers to the conclusion either that a cerebral embolism, primary site unknown, had developed or that there was an intravascular thrombosis, initiated by the marked polycythemia. The time relation of the first convulsive seizures with the administration of the insulin raised some question as to the role that the insulin might have played in the cause of this symptom complex.

The possibility of the development of a brain abscess was apparently not considered, although many features of this case were suggestive of this complication. Although no obvious focus for the origin of septic emboli could be found either clinically or pathologically, the infections of the mouth and lungs must both be considered as possible points of origin.

This case is characteristic of others in this group, illustrating the unheralded development of a cerebral abscess in a patient with the tetralogy of Fallot, with rupture of the abscess into a ventricle producing fatal meningitis.

CASE 3—A 20 year old white woman was transferred to the Boston City Hospital on July 20, 1942 from a

neighboring hospital, with the diagnosis of acute purulent meningitis and congenital heart disease.

The patient was known to have had "heart trouble" since birth, with blueness of the extremities and dyspnea on slight exertion.

At 10 years of age she had several bouts of "growing pains," but the condition was considered too minor to warrant medical consultation.

In 1934, two years later, the pain in the legs recurred, and she was admitted to the Massachusetts General Hospital, where a diagnosis was made of rheumatic heart disease superimposed on a congenital defect of the heart.

With the exception of her severe exertional dyspnea, she was asymptomatic for the next six years.

Two weeks before her last admission to the hospital, on July 20, she began to experience intermittent headaches, which became constant four days before she entered the hospital. These headaches were accompanied by nausea and projectile vomiting. Although she believed that she had had some fever, she said that she had not experienced any chills. She complained of a slight stiffness of the neck and appeared to show intermittent periods of mental confusion.

Physical Examination—On her admission she appeared restless, somewhat irrational and acutely ill. There was a definite cyanosis of the face, lips and nail beds. There was slight injection of the ear drums bilaterally, and the neck was rigid.

The heart rate was 104 with a gallop rhythm heard over the entire precordium. The pulmonic second sound was loud and snapping, with a soft, blowing systolic murmur heard along the left border of the sternum. This murmur was heard loudest at the third left interspace. The spine was hyperextended, with active resistance to attempted flexion. Kernig reflexes were elicited bilaterally. The ankle and abdominal reflexes were absent. The fingers and toes showed pronounced clubbing.

Laboratory Studies—In the time available only a lumbar puncture was performed, which yielded cloudy fluid under increased pressure, containing 330 mg of protein per hundred cubic centimeters and many white cells, chiefly polymorphonuclear leukocytes. No bacteria were seen.

Course—Her temperature continued to rise (to 105 F) despite the administration of sulfonamide compounds. Nine hours after her admission, although no growth from the culture of the spinal fluid had been obtained, an empiric intrathecal injection of antimeningococcus serum was given. She was transferred to the Boston City Hospital, department of contagious diseases, where the results of physical examination were identical with those just given, except that the blood pressure now was 60 systolic and 0 diastolic, with a weak thready, rapid pulse. Despite all supportive measures, she died within twenty-four hours.

It may be noted that at no time did a culture of the spinal fluid reveal organisms, although on one occasion gram-negative cocci were reported to have been seen on smear.

Postmortem Examination—Again the only pertinent observations related to the heart and brain. The heart weighed 350 Gm (slightly increased in size and weight). It presented, again, the complex of congenital cardiac malformations known as the tetralogy of Fallot, with a defect 1 by 1.5 cm of the interventricular septum, dextroposition of the aorta, pulmonary stenosis and cor pulmonale.

The ductus arteriosus was, likewise, widely patent. The right ventricle measured 1 cm in thickness, exactly equal to the thickness of the left ventricle.

The brain was also similar in many respects to those previously described and weighed 1,440 Gm. It was

intensely congested, showing over its sulci and vascular channels a yellow-green purulent exudate. Coronal section revealed a small abscess cavity 1 cm in transverse diameter and 5 cm in length in the left superior temporal convolution. It contained a thick green exudate enclosed in a firm, apparently fibrous wall. At one point in its extent, the abscess could be seen to communicate with the lateral ventricle and subarachnoid space (fig 2). All ventricular cavities were filled with thick purulent exudate.

Microscopic examination of the brain sections demonstrated the abscess wall to be well formed, containing many fibroblasts and newly formed blood vessels. An inflammatory tract could be seen to communicate with the lateral ventricle.

Bacteriologic Study—A smear of the exudate, while demonstrating many white blood cells, showed no organisms, and the culture of the meninges revealed no growth.

Comment—Case 3 bears a great similarity to case 1 in that in a patient with known congenital heart disease signs of meningitis insidiously developed, which rapidly led to her death. As in the previous cases, the underlying brain abscess was completely unsuspected.



Fig 2—The abscess cavity is situated in the left superior temporal gyrus and extends from the cortex almost to the body of the lateral ventricle in this plane of section.

COMMENT

It is interesting to note that in cases 1 and 3 the fatal illnesses were initiated by the insidious development of lethargy, drowsiness and headaches, progressing to signs of frank meningitis and death.

Case 2, on the contrary, was somewhat more confused by the simultaneous occurrence of diabetes and other incidental conditions. In this patient the fatal illness was initiated by sudden seizures resembling reactions to insulin, and it was not until the day before her death that meningitis became clinically apparent.

Despite the fact that in 2 cases the terminal illnesses developed insidiously and in the third somewhat acutely, all 3 cases present good illustrations of this not rare complication of congenital heart disease, namely, the development of a brain abscess. The unexpected onset in a patient with congenital heart disease of signs and symptoms pointing to a lesion of the

central nervous system of a focal type, which when untreated leads to frank meningitis and sudden death, may well indicate the development of a cerebral abscess with subsequent rupture of it into the cerebral ventricular system.

While practically all varieties of septal defects have been associated with brain abscess, the complex known as the tetralogy of Fallot is by far the most common, occurring in 10 out of 21 cases of this complication reported in the literature and in all 3 cases of this report, a total of 13 out of 24 cases.

In the cases reported here two abscesses occurred in the left side and one in the right side.

The precise pathogenesis of brain abscesses occurring in patients with septal defects of the heart is not known. However, many closely related facts which throw considerable light on the problem are known. I may begin by stating that there are only three known mechanisms by which brain abscesses may develop in any patient: (a) direct extension from some neighboring infection, such as mastoiditis or osteomyelitis of the skull, (b) retrograde thrombophlebitis from some source similar to that just mentioned and (c) some embolic phenomenon from a distant focus of infection. In the preceding cases it was definitely established that the brain abscesses could not have arisen from nearby infections, hence, it must be assumed that they were embolic in origin.

Contrary to common belief, it is now well established by the work of Malinowski⁴ and others that simple implantation of organisms into the brains of animals, either by infection of the blood stream or by direct inoculation, will not give rise to brain abscess. Equally well known is the fact that in animals abscess can be produced in the brain only by prior injury to the brain substance or its vascular supply followed by the implantation of organisms into the site of injury. Many techniques have been used by Markley,⁵ Graff,⁶ Thomas,⁷ Falconer, McFarlan and Russell⁸ and others to produce these abscesses, all of them based on the

4 Malinowski, N. Ueber kunstlich erzeugte Gehirnabscesse, *Centralbl f d med Wissensch* **29** 162, 1891.

5 Markley, G. M. A Method for the Experimental Production of Brain Abscesses, *Proc Soc Exper Biol & Med* **47** 171 (May) 1941.

6 Graff, R. A. Experimental Production of Abscess of the Brain in Cats, *Arch Neurol & Psychiat* **31** 199 (Jan) 1934.

7 Thomas, L. A Single Stage Method to Produce Brain Abscess in Cats, *Arch Path* **33** 472 (April) 1942.

8 Falconer, M. A., McFarlan, A. M., and Russell, D. S. Experimental Brain Abscesses in the Rabbit, *Brit J Surg* **30** 245 (Jan) 1943.

theory just mentioned. The agents used to produce the initial injury vary from trauma by mechanical injury to injection of sodium ricinoleate and infected agar mass, the latter agent acting both as a foreign body and as an infectious agent. The injury has been either accompanied with or followed by the direct implantation of organisms into the traumatized site. It therefore seems reasonable to assume that brain abscesses associated with septal defects of the heart must simply be a result of paradoxical emboli in the brain, either sterile or infected, producing an area of lowered resistance, followed in the former instance by bacteremia which infects the area of encephalomalacia. In this regard, it is to be hoped that study of a larger number of these cases may reveal instances of encephalomalacia prior to their infection by organisms spread through the blood stream. This hypothesis has previously been discussed by Hanna and others. Unfortunately, it has been difficult in our cases here and in most of the previously reported cases to demonstrate adequate origins for the emboli and the transient bacteremia. However, this failure does not necessarily completely invalidate this working hypothesis, because it may be impossible in certain cases to demonstrate origins for many embolic phenomena, and the bacteremia may have been so transient as to have passed entirely undetected.

In the hope that it might be possible to substantiate experimentally the assumption that abscess results from embolism followed by infection, experiments were carried out on rabbits in which attempts were made to produce focal areas of encephalomalacia by injection of particulate matter into the internal carotid artery, followed in ten to twelve days by the intravenous

injection of virulent cultures of organisms. These experiments were similar to the work of Graff. Inasmuch as great difficulty was encountered in the production of small focal infarcts with these technics, I attempted to traumatize the brain substance directly by instrumentation and injection of sodium ricinoleate and followed this at an interval by the intravenous injection of virulent cultures of *Staph aureus*, *Escherichia coli* and alpha hemolytic streptococci. These attempts, as were those of Stewart cited by Graff,⁶ were all unsuccessful, inasmuch as the areas of injury did not become abscessed. However, the number of experiments performed was too few to permit final decision, and more work is in progress along this line.

SUMMARY AND CONCLUSION

Three cases of cerebral abscess complicating congenital septal defects of the heart are added to those previously reported, bringing the total number of such cases in the literature to date to 26. In only 3 cases in the literature has an antemortem diagnosis of the disease been made and surgical drainage been instituted, a proportion which reflects principally the difficulty in diagnosis, arising in most instances from unfamiliarity with this complication of septal defects of the heart.

With the increased number of cases reported, it is to be hoped that in patients with congenital heart disease, especially in those having the tetralogy of Fallot, underlying brain abscess will be considered in the diagnosis of any focal neurologic damage or meningitis. Certainly only early recognition will permit successful surgical intervention and hope for cure of this uncommon syndrome.

INFLUENCE OF ANOXEMIA ON THE HEMOPOIETIC ACTIVITY

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The exact mechanism responsible for the maintenance of an equilibrium between production and destruction of blood in the normal person is not entirely understood, but it has become an almost established fact that the oxygen tension of the circulating blood is an important factor in regulating the degree of hemopoietic activity. Since the observations of Bert¹ and Viault,² in the second half of the last century, it has been customary to refer to the polycythemia found in human beings and animals exposed to a low barometric pressure as the classic example of the stimulating effect of oxygen deficiency on erythrocyte and hemoglobin formation. The demonstration by Barcroft and his collaborators³ in 1923 that newcomers and residents at high altitudes exhibit a lowering of the arterial oxygen saturation as a consequence of the low oxygen tension in the inspired air opened a most fertile field for the accurate study of the relationship between the degree of anoxia and the hematologic response. However, the opportunity has not been adequately appreciated, and most studies at high altitudes have been carried out on human beings or animals subjected for only a few hours or days to such an abnormal environment. It does not need to be emphasized that the results obtained in these observations, as well as in short time experiments in chambers where the pressure or the percentage of oxygen is artificially lowered, do not reveal the true nature of the processes of hematologic adaptation to a constant or intermittent deficiency in the oxygen supply to the tissues. The degree as well as the duration and constancy of the anoxic stimulus must play a part in in-

fluencing the hemopoietic activity. A more ample knowledge of these modifying factors not only may be of value from the point of view of exposure to a low barometric pressure but may help to clarify some related clinical problems. Anoxia in one form or another is an alteration common to many pulmonary, circulatory, hematic and other diseases in which the blood findings have been partially or totally related to the disturbance in respiratory function. In other processes, like polycythemia vera, anoxia is suspected to have an important etiologic role, but conclusive proof has not been afforded yet.

The investigations to be reported in this paper concern the morphologic and other characteristics of the circulating blood under the influence of temporary, intermittent and chronic anoxic anoxia (anoxemia). Most of the work has been carried out at high altitudes (chart 1), and the results obtained have been compared with those observed in the study of healthy subjects at sea level and in previous related investigations. No attempt has been made to cover all the vast literature accumulated in this field, which has been recently summarized by Van Liere.⁴

METHODS

All determinations have been made on blood taken in the morning while the subject was fasting or after he had eaten a light breakfast. Fifteen to twenty cubic centimeters of blood was obtained from a venous puncture, care being taken to release the tourniquet as soon as the needle was introduced, and 5 cc was transferred to a small bottle containing 10 mg of potassium oxalate in powder. The rest of the blood was utilized for the determination of the serum bilirubin in its total amount⁵ or in fractionated forms, for the latter investigation the Malloy-Evelyn photoelectric colorimetric procedure⁶ was used, and the serum proteins by means of the refractometric index and the Kagan falling drop method.⁷ On the 5 cc of oxalated blood the following determinations were made: (a) number of erythrocytes and of leukocytes per cubic millimeter, a double Neubauer counting chamber being used, and the average of two counts taken as the final result, (b) number of reticulocytes (per hundred red cells and per cubic

Aided by a grant from the Rockefeller Foundation.
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Read in part by Dr Hurtado at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N J, June 8, 1942.

1 Bert, P. *La pression barometrique*, Paris, G Masson, 1878.

2 Viault, E. *Compt rend Acad d sc* **112** 295, 1891.

3 Barcroft, J, Binger, C H, Bock, A V, Duggart, J H, Forbes, H S, Harrop, G, Meakins, J C, and Redfield A C. *Tr Roy Soc, London, s B* **211** 351, 1923.

4 Van Liere, E J. *Anoxia Its Effect on the Body*, Chicago, University of Chicago Press, 1942.

5 Barron, E S G. *Medicine* **10** 77, 1931.

6 Malloy, H T, and Evelyn, K. *J Biol Chem* **119** 481, 1937.

7 Kagan, B M. *J Clin Investigation* **17** 373, 1938.

millimeter), brilliant cresyl blue being used as stain, (c) the hematocrit value, measured with a Wintrobe tube which was centrifuged for forty-five to sixty minutes at about 3,000 revolutions per minute in an International size 1 type SB centrifuge (the hematocrit figure was multiplied by 1.09 to correct for the shrinkage due to the anticoagulant used), and (d) hemoglobin (grams per hundred cubic centimeters), estimated either by measuring the oxygen-combining capacity of the blood in the Van Slyke manometric apparatus⁸ or by employing the Evelyn photoelectric colorimeter previously calibrated with the former method. Capillary blood was obtained immediately after the venous puncture, from a finger or the lobe of the ear. From this sample a smear was made and stained with Wright's stain, this was used for the determination of the differential leukocyte count, according to Schilling's scheme,⁹ and for the measurement of the diameter (microns) of the red cells. For the latter determination a calibrated ocular micrometer was used. A total of 300 cells were measured in each case, with the exception of some studied at the highest altitude, in which only 100 to 200 cells were measured, owing to the difficulties of obtaining an adequate smear. For a few subjects these investigations were made on the sample of venous blood. The mean corpuscular volume (cubic microns), the mean corpuscular hemoglobin (micromicrograms) and the mean corpuscular hemoglobin concentration (per cent) were calculated according to Wintrobe's formulas¹⁰. The mean corpuscular thickness (microns) was calculated, indirectly, by means of the formula

$$\frac{\text{mean corpuscular volume}}{3.1416 \times \left(\frac{D}{2}\right)^2}$$

in which D equals the mean corpuscular diameter. The mean corpuscular surface area (square microns) was calculated from the formula

$$\left(\frac{V}{T} \times 2\right) + (3.1416 \times T \times D)$$

in which V represents the mean corpuscular volume, T the mean corpuscular thickness and D the mean corpuscular diameter. The spherocytic index was derived from Heilmeyer's¹¹ formula, $\frac{\text{mean corpuscular thickness}}{\text{mean corpuscular diameter}}$

The fragility of the red cells to hypotonic solutions of sodium chloride was studied in some subjects by the method of Giffin and Sanford¹². At high altitudes the viscosity of the blood was determined by means of a Hess viscosimeter and distilled water for comparison. In a few cases the gastric acid content was investigated, 50 cc of a 7 per cent alcoholic solution orally administered and a subcutaneous injection of 0.5 cc of histamine phosphate solution being used as stimulants for the gastric mucosa.

The total circulating blood volume was determined in most cases by the method of Keith, Rowntree and Geraghty,¹³ with the modifications of Hooper, Smith,

Belt and Whipple.¹⁴ A 15 per cent solution of brilliant vital red was employed. In a smaller group of cases, at sea level and at high altitudes, Evans blue was employed in the determination, according to the technic of Gibson and Evans.¹⁵ Five samples of blood were obtained at known intervals after the injection, and the concentration of the dye was observed by means of the Evelyn photoelectric colorimeter, with use of the microabsorption cell described by Evelyn and Gibson.¹⁶ The carbon dioxide content and the oxygen saturation of the arterial blood were determined in blood obtained, with the usual precautions to avoid exposure to the air, from the radial artery. The blood was kept under mercury and at a low temperature when several hours elapsed before the analysis. The determinations were carried out according to the method of Van Slyke and Neill⁸ in their manometric apparatus.

NORMAL HEMATOLOGIC VALUES AT SEA LEVEL

A considerable number of observations made on healthy male adults in different parts of the world, which have been reviewed by several investigators¹⁷ and are summarized in table 1, have demonstrated that there are not definite geographic or racial differences at sea level in regard to the number of red cells and the amount of hemoglobin in the circulating blood, a fact pointed out by Wintrobe^{17a} some years ago. We have made observations on 200 healthy men living in Lima, at sea level.¹⁸ The results obtained for half of these subjects have already been published.¹⁹ Most of the men studied were medical students, and a few belonged to the army, their ages varied between 19 and 45 years, with the large majority between 20 and 30 years. Ninety of the men had been born and raised at sea level, and 110 were natives of places located at altitudes over 2,000 meters (7,560 feet) and had lived at sea level for periods varying from six months to many years. In the analysis of the collected data no appreciable difference was found between the values for men born at sea level and

14 Hooper, C. W., Smith, H. P., Belt, A. E., and Whipple, G. H. *Am J Physiol* **51**: 205, 1920.

15 Gibson, J. G., and Evans, W. A. *J Clin Investigation* **16**: 301, 1937.

16 Evelyn, K., and Gibson, J. G. *J Biol Chem* **122**: 391, 1938.

17 (a) Wintrobe, M. M. *Bull Johns Hopkins Hosp* **53**: 118, 1933. (b) Nelson, C. F., and Stoker, R. *Folia haemat* **58**: 333, 1937. (c) Isaacs, R. *The Erythrocyte in Downey, H. Handbook of Hematology*, New York, Paul H. Hoeber, Inc., 1938. (d) Myers, C. V., and Eddy, H. M. *J Lab & Clin Med* **24**: 502, 1939. (e) Meccheri, L. A. *Publ d Centro de invest fisiol* **4**: 83, 1940. (f) Wardlaw, H. S. H. *M J Australia* **2**: 103, 1941. (g) Hamre, C. J., and Au, M. H. *J Lab & Clin Med* **27**: 1231, 1942.

18 Lima is located at an altitude of 150 meters (490 feet), from the point of view of the studies reported in this paper, this may be considered as sea level.

19 Hurtado, A., Pons, M. J., and Merino, M. C. *La anemia de la enfermedad de Carrion, Lima Peru*, Libreria e Imprenta G. I. 1938.

8 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry II Methods*, Baltimore, Williams & Wilkins Company, 1932.

9 Schilling, V. *El cuadro hemático y su valor en la clínica*, Barcelona, Editorial Labor, 1931.

10 Wintrobe, M. M. *J Lab & Clin Med* **17**: 889, 1932.

11 Heilmeyer, L. *Deutsches Arch f klin Med* **17**: 292, 1936.

12 Todd, J. C. *Clinical Diagnosis by Laboratory Methods*, Philadelphia, W. B. Saunders Company, 1923.

13 Keith, N. M., Rowntree, L. G., and Geraghty, J. T. *A Method for the Determination of Plasma and Blood Volume*, *Arch Int Med* **16**: 547 (Oct) 1915.

those for men born in high localities, provided that the latter had been living at sea level for a prolonged time In consequence the findings for both groups are given together in table 2 On the other hand, men who had been born at high altitudes and had been living in Lima for only a few months frequently showed a moderate reduction in red cells and hemoglobin For this reason obtained in different parts of the world, and the statistical variations are not higher than the ones ordinarily found in such determinations The values corresponding to some of the morphologic characteristics of the circulating erythrocyte (mean corpuscular volume, hemoglobin and hemoglobin concentration) also agree closely with those observed by Wintrobe²⁰ and other

TABLE 1—Average Values for Red Blood Cells and Hemoglobin at Sea Level in Healthy Men Summary of Literature Reviewed by Several Authors¹⁷

Investigators	Place	Number of Subjects	Red Blood Cells, Millions per Cu Mm	Hemoglobin, Gm per 100 Cc
Goldhamer and Fritzell	U S A	100	4 72	14 0
Walters	U S A	100	4 84	15 1
Emerson	U S A	171	5 44	15 1
Wintrobe and Miller	U S A	100	5 85	17 0
Wintrobe	U S A	86	5 48	16 0
Haden	U S A	70	4 95	15 3
Osgood	U S A	259	5 42	15 8
Osgood and others	U S A	137	5 39	15 8
Foster and Johnson	U S A	115	5 26	15 6
Isaacs and Fritzell	U S A	57	5 08	15 2
Sachs, Levine and Fabian	U S A	100	4 88	15 0
Nelson and Stoker	U S A	350	5 11	15 0
Broun and Briggs	U S A	23	5 29	16 6
Epstein	U S A	42	4 93	
Williamson	U S A	140		17 0
Williamson	U S A	81		15 8
Dill	U S A	40		15 5
Price Jones	U S A	20		15 4
Haden	U S A	20		15 2
Haden	U S A	20		15 8
Myers and Eddy	U S A	111		15 7
Rowntree and Brown	U S A	49		16 4
Kaltreider, Hurtado and Brooks	U S A	25		16 2
Fiddes and Whitney	Canada	20	5 52	15 6
Parodi	Argentina	50	5 50	15 4
Tenconi	Argentina	50	5 30	14 8
Orias	Argentina	82		15 3
Orias	Argentina	321		14 3
Orias	Argentina	307		14 6
Gargiulo	Argentina	51		15 6
Gargiulo	Argentina	944		15 2
Gargiulo	Argentina	128		17 0
Meccheri	Argentina	227		15 4
Hurtado, Pons and Merino	Peru	100	5 26	15 7
Price-Jones, Vaughan and Goddard	England	100	5 50	14 5
Price Jones and others	England	100	5 43	14 5
McGeorge	England	50	5 48	15 2
Jenkins and Don	England	116		15 8
Bing	Denmark	22	6 10	
Beltring and Sorensen	Denmark	60		14 9
Jervell and Waaler	Norway	50	5 52	16 2
Linnbergh and others	Norway	51	5 27	
Burgi	Switzerland	224	5 00	15 0
Millet and Balle Helaers	Belgium	60	3 90	13 3
Jimenez Diaz	Spain	18	4 88	
Ales	Spain	40		14 9
Komocki	Poland	33	5 84	
Heilmeyer and Hansold	Germany	40	5 06	15 9
Horneffer	Germany	40	4 96	16 0
Napier and Das Gupta	India	50	5 36	14 8
Solkei and others	India	121	5 11	15 4
Sankaran and Rajagopal	India	125		16 7
Napier and Nanjundar	India	25		12 6
Chia Tu Tien	China	320	5 12	
Hamre and Man Hing Au	Hawaii	137	5 08	15 1
Chamberlain	Philippine Islands	687	5 20	
Navarro	Philippine Islands	104		14 1
Wardlaw and others	Australia	25		15 1
Wardlaw	Australia	26		15 8
Grand mean ± P E			5 23 ± 0 04	15 4 ± 0 07

the results obtained for 25 natives of high altitudes with a period of residence at sea level of less than a year have been separately summarized (table 3)

The mean values for number of red blood cells per cubic millimeter, grams of hemoglobin per hundred cubic centimeters and hematocrit level (percentage of red cells) in the blood of the series of 175 healthy men are similar to those investigators^{17c} There is some discrepancy in the results found by several workers in regard to the normal diameter of the red blood cells The related literature has been summarized by Price-

20 Wintrobe, M M Anemia Classification and Treatment on Basis of Differences in Average Volume and Hemoglobin Content of Red Corpuscles, Arch Int. Med 54 256 (Aug) 1934

Jones²¹ and recently by Isaacs^{17c} The mean observed values vary between 7.20 and 7.90 microns (measured in dry stained preparations) Our mean value of 7.48 ± 0.01 microns falls within the accepted normal limits of variation The coefficient of variation of 2.0 per cent indicates an extremely small fluctuation of the mean

shek and Singer²³ have indicated a normal range of 1.9 to 2.4 microns Our mean value, of 2.09 ± 0.01 microns, relates closely to such findings, but it is higher than the low values reported by Emmons²⁴ and Gram,²⁵ who used entirely different methods in the measurement Guest and Wing²⁶ and Bernstein and Chesluk²⁷ recently

TABLE 2—Observations on Blood of Healthy Men at Sea Level

Determinations	Number of Subjects	Mean \pm P E	St Dev \pm P E	Coefficient of Variation (%)	Extreme Variations
Red blood cells (millions per cu mm)	175	5.14 ± 0.02	0.34 ± 0.01	6.6	4.32 - 5.90
Hematocrit (red cells, per cent)	175	46.8 ± 0.11	2.3 ± 0.03	4.9	41.0 - 52.7
Hemoglobin (grams per 100 cc)	175	16.00 ± 0.04	0.80 ± 0.03	5.0	13.96 - 18.30
Corpuscular mean volume (cu microns)	175	91.3 ± 0.23	4.5 ± 0.16	4.9	77.8 - 103.1
Corpuscular mean diameter (microns)	130	7.48 ± 0.01	0.15 ± 0.01	2.0	7.10 - 7.85
Corpuscular mean thickness (microns)	130	2.09 ± 0.01	0.12 ± 0.01	5.7	1.75 - 2.43
Corpuscular mean surface area (sq microns)	130	136.7 ± 0.22	3.8 ± 0.14	2.8	126.3 - 145.3
Spherocytic index	130	0.28 ± 0.01	0.01 ± 0.004	3.6	0.23 - 0.33
Corpuscular mean hemoglobin (micromicrograms)	175	31.2 ± 0.09	1.9 ± 0.06	6.1	27.0 - 35.5
Corpuscular mean hemoglobin concentration (per cent)	175	34.1 ± 0.07	1.4 ± 0.05	4.1	30.9 - 37.4
Reticulocytes (per cent)	93	0.5 ± 0.02	0.3 ± 0.01	60.0	0 - 1.2
Reticulocytes (thousands per cu mm)	93	18.4 ± 0.94	13.4 ± 0.66	72.8	0 - 61.1
Red blood cell fragility					
Initial hemolysis (per cent)	38	0.46 ± 0.001	0.01 ± 0.001	2.2	0.48 - 0.40
Total hemolysis (per cent)	38	0.38 ± 0.002	0.02 ± 0.001	5.2	0.40 - 0.34
Bilirubin, total* (mg per 100 cc)	93	0.76 ± 0.03	0.33 ± 0.02	43.4	0.41 - 1.61
Bilirubin, total† (mg per 100 cc)	92	0.72 ± 0.02	0.27 ± 0.01	37.5	0.26 - 1.44
Bilirubin, direct† (mg per 100 cc)	92	0.37 ± 0.01	0.15 ± 0.01	40.5	0.13 - 0.94
Bilirubin, indirect† (mg per 100 cc)	92	0.35 ± 0.01	0.16 ± 0.01	45.7	0.04 - 0.96
Leukocytes (number per cu mm)	167	$6,800 \pm 77$	$1,480 \pm 54$	21.8	3,480 - 14,840
Differential leukocyte count	70				
Neutrophils, stab (per cent)		2.6 ± 0.10	1.3 ± 0.07	50.0	0 - 6
Neutrophils, segmented (per cent)		55.1 ± 0.58	7.3 ± 0.41	13.2	38 - 70
Neutrophils, total (per cent)		57.8 ± 0.63	7.9 ± 0.45	13.7	38 - 72
Eosinophils (per cent)		4.2 ± 0.23	2.9 ± 0.17	69.0	0 - 15
Basophils (per cent)		0.6 ± 0.04	0.6 ± 0.03	100.0	0 - 2
Monocytes (per cent)		7.2 ± 0.20	2.5 ± 0.14	34	2 - 14.5
Lymphocytes (per cent)		29.8 ± 0.47	5.9 ± 0.34	19.8	18 - 49

* Colorimetric determination using a cobalt solution as standard⁵

† Photoelectric colorimetric determination, technic of Malloy-Evelyn⁶

TABLE 3—Observations on Blood of Healthy Adult Men Born at High Altitudes and Studied at Sea Level After a Residence of Six Months to a Year

Determinations	Number of Subjects	Mean \pm P E	St Dev \pm P E	Coefficient of Variation (%)	Extreme Variations
Red blood cells (millions per cu mm)	25	5.00 ± 0.04	0.32 ± 0.03	6.4	4.46 - 5.85
Hematocrit (red cells, per cent)	25	44.0 ± 0.32	2.4 ± 0.23	5.4	37.5 - 49.1
Hemoglobin (grams per 100 cc)	25	14.70 ± 0.13	1.00 ± 0.09	6.8	12.26 - 17.00
Corpuscular mean volume (cu microns)	25	88.8 ± 0.62	4.6 ± 0.44	5.2	75.9 - 96.3
Corpuscular mean diameter (microns)	20	7.46 ± 0.03	0.20 ± 0.02	2.7	7.11 - 7.81
Corpuscular mean thickness (microns)	20	2.02 ± 0.02	0.11 ± 0.01	5.4	1.83 - 2.28
Corpuscular mean surface area (sq microns)	20	133.6 ± 0.75	5.0 ± 0.53	3.7	124.7 - 143.5
Spherocytic index	20	0.28 ± 0.003	0.02 ± 0.002	7.1	0.21 - 0.32
Corpuscular mean hemoglobin (micromicrograms)	25	29.6 ± 0.29	2.2 ± 0.21	7.4	25.7 - 33.5
Corpuscular mean hemoglobin concentration (per cent)	25	33.4 ± 0.16	1.2 ± 0.11	3.6	31.7 - 36.3

corpuscular diameter in healthy men There are few observations in the literature concerning the thickness, surface area and spherocytic index of normal red blood cells Price-Jones, Vaughan and Goddard,²² following a technic similar to the one used by us, found a mean corpuscular thickness of 2.14 microns in 100 healthy men, and Dame-

found average values of 139.7 and 135.5 square microns, respectively, for the mean corpuscular

23 Dameshek, W, and Singer, K Familial Non-hemolytic Jaundice Constitutional Hepatic Dysfunction with Indirect van den Bergh Reaction, Arch Int Med 67 259 (Feb) 1941

24 Emmons, W F J Physiol 64 215, 1927

25 Gram, H C Acta med Scandinau 66 295, 1927

26 Guest, G M, and Wing, M J Clin Investigation 21 257, 1942

27 Bernstein, M, and Chesluk, H M J Lab & Clin Med 27 1280 1942

21 Price-Jones, C Red Blood Cells Diameter, London, Oxford University Press, 1933

22 Price-Jones, C, Vaughan, J M, and Goddard, H M J Path & Bact 40 503, 1935

surface area, figures which approximate our mean value, of 1367 ± 0.22 . It is interesting that this measurement, which is indirect and derived from others, has in our series of normal men a low coefficient of variation (2.8 per cent). Dameshek and Singer²³ have given the values of 0.25 to 0.33 as the normal range for the spherocytic index, our mean value of 0.28 ± 0.01 falls within this range.

We have observed in the series of healthy men studied at sea level that the variations in some of the morphologic characteristics of the circulating erythrocytes are related to the number of these cells per cubic millimeter (table 4). Although these variations are small and within the normal range, the observed relationship is of interest in connection with the findings at high altitudes, which will be discussed in another section.

There is some variation in the results obtained by several investigators in regard to the normal number of reticulated red cells in the peripheral blood, but with the exception of Osgood, Baker

of view of previous investigations, on account of the lack of uniformity among the reported values for the normal concentration of bilirubin, which has been estimated to vary between 0.10 and 3.50 mg per hundred cubic centimeters²⁹, most investigators have, however, shown a tendency to consider 1.00 mg as the upper normal limit of variation. In our series of determinations this limit was frequently exceeded, of a total of 185 apparently healthy men investigated, 24, or 13 per cent, had a serum bilirubin above 1.00 mg. According to studies made by one of us (E. D.),³⁰ it is likely that these high bilirubin values observed at times in the blood of apparently normal subjects are due in most cases to an insufficiency of the liver in its function of excreting pigment. If this is confirmed, the range of bilirubin concentration in the plasma considered normal will have to be considerably reduced. Cantarow and others³¹ have found that the direct bilirubin constitutes about 35 to 70 per cent of the total amount, with absolute values between 0.15 and 0.35 mg. Our mean value of 0.37 ± 0.01 and the standard deviation of 0.15 mg are distinctly higher.

In regard to the fragility of the red blood cells to hypotonic solutions of sodium chloride, we obtained the mean values of 0.46 ± 0.001 and 0.38 ± 0.002 per cent for initial and total hemolysis, respectively, in determinations made for 38 of our subjects. Daland and Worthley,³² in an investigation made on 20 normal adults, observed the first traces of hemolysis at concentrations of 0.44 to 0.47 per cent and its completion at 0.27 per cent, the latter low figure is probably accounted for by the microscopic technic employed.

The great variations which are frequently observed in apparently healthy subjects in regard to the number of leukocytes in the circulating blood have been emphasized by Garrey and Brown.³³ We have not observed the extreme

TABLE 4—*Relationship Between the Number and the Morphologic Characteristics of the Red Blood Cells (Observations on 175 Healthy Men at Sea Level)*

Red Blood Cells, Millions per Cu Mm	Number of Subjects	Corpuscular Mean Volume $\pm P. E.$, Cu Microns	Corpuscular Mean Hb $\pm P. E.$, Micro micrograms	Corpuscular Mean Hb Concentration $\pm P. E.$, per Cent
4.00 - 4.49	7	93.2 ± 0.88	34.1 ± 0.21	34.7 ± 0.16
4.50 - 4.99	48	94.8 ± 0.17	32.8 ± 0.15	34.6 ± 0.10
5.00 - 5.49	92	90.2 ± 0.22	30.7 ± 0.10	34.0 ± 0.10
5.50 - 5.99	28	87.1 ± 0.46	29.4 ± 0.15	33.6 ± 0.17

and Wilhelm,²⁸ who found a mean value of 1.5 per cent, all observed averages have been under 1 per cent, this being considered by most workers as the upper normal limit of variation. Our mean values of 0.5 ± 0.02 per cent and 18.4 ± 0.94 thousand per cubic millimeter, obtained for 93 men, are in agreement with such previous findings.

The serum bilirubin has been determined for 93 subjects in its total amount, by means of a colorimetric procedure and with a cobalt solution used as a standard for comparison,⁵ and for another group, of 92 men, in its fractionated forms, direct and indirect, by the recently introduced photoelectric colorimetric method of Malloy and Evelyn.⁶ There is a close agreement between the mean values of 0.76 ± 0.03 and 0.72 ± 0.02 mg per hundred cubic centimeters obtained by these methods, respectively, for the total amount of bilirubin in the serum. It is difficult to evaluate these figures from the point

29 von den Bergh, H. Die Gallenfarbstoffe in Blute, Leipzig, 1918. Haselhorst, G. Munchen med Wehnschr 68 174, 1921. Forster, J. Klin Wehnschr 4 1689, 1925. Perkins, F. S. Blood Bilirubin Estimation and Clinical Significance, Arch Int Med 40 195 (Aug) 1927. Vaughan, J. M., and Haslewood, G. A. D. Lancet 1 133, 1938. Abels, J. C., Rekers, P. E., Binkley, G. E., Pack, J. T., and Rhoads, C. P. Ann Int Med 16 221, 1942. Lopez Garcia, A., and Zelasco J. F. An d Inst d invest fis apl a la pat humana 3 89, 1941.

30 Delgado, E. Estudios sobre bilirrubina, Lima, Facultad de Medicina, 1943.

31 Cantarow, A., Wirts, C. W., Jr., and Hollander, G. Quantitative Studies of Direct-Reacting Serum Bilirubin, Arch Int Med 69 986 (June) 1942.

32 Daland, G. A., and Worthley, K. J. Lab & Clin Med 20 1122, 1935.

33 Garrey, W. F., and Brown, R. W. Physiol Rev 15 597, 1935.

28 Osgood, E. E., Baker, R. L., and Wilhelm, M. M. Am J Clin Path 4 292, 1934.

fluctuations found by some investigators³⁴ Our mean value, of $6,800 \pm 77$, leukocytes per cubic millimeter, and the standard deviation, of 1,480, are almost identical with those observed by Price-Jones, Vaughan and Goddard²² in 100 men in England and by Osgood and others³⁵ in 198 men

Table 5 summarizes the mean values obtained by several investigators³⁶ in the determination of the circulating blood volume of healthy men, by means of various dye methods Our findings consisting of values for 36 subjects, for 26 of whom the determination was made with brilliant

TABLE 5—*Determinations of Blood Volume in Healthy Men (by Dye Methods) at Sea Level and in Different Parts of the World—Summary of Literature*³⁶

Investigators	Place	Dye Used	Number of Subjects	Blood, Cc per Kg, Average Values	Plasma, Cc per Kg, Average Values
Rowntree and Brown	U S A	Oongo v red	49	83.6	51.0
Gibson and Evans	U S A	Evans blue	49	77.7	44.7
Looney and Freeman	U S A	Oongo red	29	81.4	41.1
Kaltreider, Hurtado and Brooks	U S A	Brilliant vital red	25	79.1	42.8
Sparks and Haden	U S A	Congo red	10	64.9	34.4
Goldbloom and Libin	U S A	Trypan red	10	78.4	40.5
Hallock	U S A	Evans blue	10	89.5	46.4
Levin	Argentina	Vital red	56	78.0	42.0
Hurtado, Pons and Merino	Peru	Brilliant vital red	15	87.8	47.8
Davis	England	Evans blue	11	76.7	40.5
Menderhaussen	Germany	Congo red	16	71.7	39.0
Rusznayk	Germany	Trypan red	8	83.3	44.7
Uhlenbruck	Germany	Congo red	7	79.6	41.4
Seyderhelm and Lampe	Germany	Trypan red	6	84.7	44.1
Grand mean \pm P E				80.1 ± 1.20	43.1 ± 0.72

TABLE 6—*Determinations of Blood Volume (by Dye Methods) in Healthy Men at Sea Level*

	Mean \pm P E	St Dev \pm P E	Coefficient of Variations (%)	Extreme Variations
With Brilliant Vital Red (26 Subjects)				
Blood volume (liters)	5.21 ± 0.10	0.79 ± 0.07	15.2	3.96 - 6.60
Blood volume (cc per Kg)	86.5 ± 1.10	8.3 ± 0.77	9.6	72.2 - 106.4
Plasma volume (liters)	2.82 ± 0.06	0.43 ± 0.04	15.2	2.10 - 3.77
Plasma volume (cc per Kg)	47.1 ± 0.59	4.5 ± 0.42	9.6	36.3 - 56.4
Red cell volume (liters)	2.34 ± 0.03	0.36 ± 0.03	15.4	1.75 - 3.11
Red cell volume (cc per Kg)	38.8 ± 0.59	4.5 ± 0.42	11.6	30.8 - 47.0
Total hemoglobin (grams)	788 ± 14.8	112 ± 10.4	14.2	604 - 1,059
Total hemoglobin (Gm per Kg)	13.2 ± 0.18	1.4 ± 0.12	10.6	10.1 - 15.3
With Evans Blue (10 Subjects)				
Blood volume (liters)	5.02 ± 0.19	0.85 ± 0.13	16.9	4.12 - 6.57
Blood volume (cc per Kg)	85.4 ± 1.28	5.7 ± 0.90	6.7	76.7 - 96.6
Plasma volume (liters)	2.70 ± 0.08	0.37 ± 0.05	13.7	2.21 - 3.47
Plasma volume (cc per Kg)	46.2 ± 1.03	4.6 ± 0.73	9.9	38.6 - 55.1
Red cell volume (liters)	2.29 ± 0.10	0.43 ± 0.07	18.8	1.73 - 3.21
Red cell volume (cc per Kg)	39.0 ± 0.49	2.2 ± 0.35	5.6	35.7 - 43.8
Total hemoglobin (grams)	779 ± 28.6	127 ± 20.2	16.3	633 - 1,057
Total hemoglobin (Gm per Kg)	13.3 ± 0.18	0.8 ± 0.12	6.0	12.0 - 14.5

in the United States The differential leukocyte count, determined for 70 of our subjects, gave values which agree with those indicated by Schilling⁹ but which are slightly different, in the percentage of stab neutrophils, eosinophils, monocytes and lymphocytes, from the findings of Osgood and others³⁵

34 (a) Feinblatt, H M Alimentary Leukocytosis in Eighty Normal Men, *J A M A* **80** 613 (March 3) 1923 (b) Sabin, F R, Cunningham, R S, Doan, C A, and Kindwall, S A *Bull Johns Hopkins Hosp* **37** 14, 1925 (c) Looney, J M, and Freeman, H Volume of Blood in Normal Subjects and in Patients with Schizophrenia, *Arch Neurol & Psychiat* **34** 956 (Nov) 1935

35 Osgood, E E, Brownlee, I E, Osgood, M W, Ellis, D M, and Cohen, W Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates Determined for Healthy Persons 19 Years of Age and Older, *Arch Int Med* **64** 105 (July) 1939

36 (a) Looney and Freeman^{34c} Menderhaussen, A *Ztschr f klin Med* **97** 468, 1923 (b) Seyderhelm, R, and Lange, W *Ztschr f d ges exper Med* **35** 177 1923 (c) Rusznayk, S *Deutsches Arch f klin Med* **157** 186, 1927 (d) Rowntree, L G, and Brown, G E *The Volume of the Blood and Plasma in Health and Disease*, Philadelphia, W B Saunders Company, 1924 (e) Uhlenbruck, P, and Vogels *Ztschr f klin Med* **118** 172, 1931 (f) Sparks, M I, and Haden, R L *Am J M Sc* **184** 753, 1932 (g) Kaltreider, N L, Hurtado, A, and Brooks, W D W *J Clin Investigation* **13** 999, 1934 (h) Goldbloom, A A, and Libin, I *Clinical Studies in Circulatory Adjustments Clinical Evaluation of Studies of Circulating Blood Volume*, *Arch Int Med* **55** 484 (March) 1935 (i) Gibson, J G, and Evans, W A *J Clin Investigation* **16** 317, 1937 (j) Levin, E *El volumen de la sangre circulante*, Buenos Aires, El Ateneo, 1938 (k) Hallock, P *Proc Soc Exper Biol & Med* **44** 11 1940 (l) Davis, L J *Edinburgh M J* **49** 465 1942

vital red³⁷ and for 10 by the recently introduced method using Evans blue,³⁸ are given in table 6. The study of these tables reveals a rather close similarity among the various listed mean values and suggests that, at least in healthy subjects, the results obtained by the older and the newer dye methods are fundamentally alike^{38a}. It must be indicated, however, that the studies of Smith, Arnold and Whipple³⁹ and of Stead and Ebert,⁴⁰ who have pointed out that the cell-plasma ratio of the venous blood does not necessarily represent that of the entire circulation, have raised an objection, common to all dye methods, to the use of the hematocrit as a basis for the calculation of the total blood volume.

in Lima (at sea level) after a residence of less than one year in this place (table 3) shows a moderate, but definite, decrease in the number of red cells and the amount of hemoglobin in the latter group, this is not accompanied by alterations in the morphologic characteristics of the erythrocytes.

INFLUENCE OF TEMPORARY ANOXEMIA

It has been repeatedly observed that a temporary anoxemia brought about by a lowered oxygen tension in the inspired air or by interference with the mechanisms responsible for the acquisition of this gas at lung level is followed in

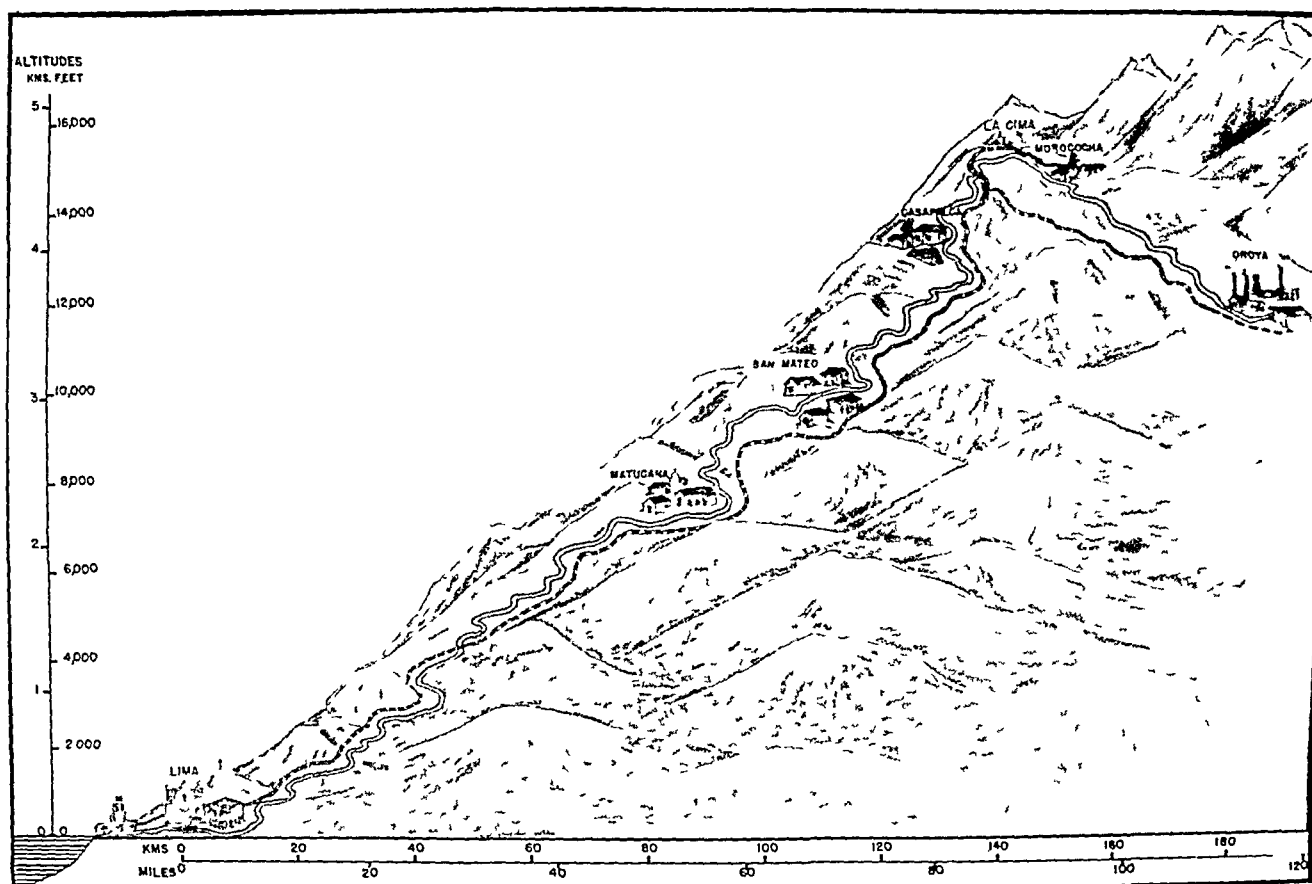


Chart 1—Altitudes and location of the different places where the hematologic studies were carried out (zone located on the western slope of the Andes in the central region of Peru)

Comparison of the results obtained in the study of the 175 normal men with those for the group of 25 men born at high altitudes and investigated

37 Keith, Rowntree and Geraghty¹³ Hooper, Smith, Belt and Whipple¹⁴

38 Gibson and Evans¹⁵ Evelyn and Gibson¹⁶

38a A statistical study of the several series of observations found in the literature concerning the plasma volume in healthy men shows the same degree of variation in the results obtained with the older and the newer dye methods (brilliant vital red and Evans' blue, respectively)

39 Smith, H. P., Arnold, H. R., and Whipple, G. H. *Am J Physiol* 56 1921, 1921

40 Ebert, R. V., and Stead, E. A. *J Clin Investigation* 20 317, 1941

most cases by an increase in the number of red cells and the amount of hemoglobin in the circulating blood. There are, however, pronounced individual variations in the polycythemic response, which may be related to the degree and duration of the anoxic stimulus and to individual factors not yet well understood. We have taken four different groups of healthy men (total 67) to altitudes of 2,390 meters (7,920 feet), 3,140 meters (10,300 feet), 4,165 meters (13,660 feet) and 4,835 meters (15,860 feet). Most of the subjects were medical students, of ages between 20 and 32 years, 36 were natives of sea level localities and 31 had been born in places located at altitudes over 2,000 meters (7,660 feet) but

with a residence of one or more years at sea level previous to the investigation. Blood was obtained at sea level immediately before the ascent and again within the first two hours after arrival at the given altitude. From 12 men, 3 in each of the high altitude places, the sample of blood was taken after three hours of moderate physical activity (walking). In addition, a fifth group, of

and 4,835 meters respectively. There was no relationship between the degree of increase in hemoglobin and the place of birth of the men studied, at the two highest places we observed average increases of 0.46 and 0.49 Gm per hundred cubic centimeters of blood in men who had been born at sea level and at high altitudes, respectively.

TABLE 7—Degree of Anoxemia in Relation to Results of Hematologic Studies Made on Arrival at Places of High Altitude

Place	Altitude		Average Barometric Pressure, Mm Hg	Number of Subjects	Arterial Oxygen Saturation, per Cent *	
	Meters	Feet			Mean \pm P E	Extremo Variations
Matucana	2,390	7,920	581.4	5	91.0 \pm 0.57	88.2 - 93.0
San Mateo	3,140	10,300	530.5	5	89.6 \pm 0.74	86.2 - 92.5
Casapalca	4,165	13,660	470.8	5	80.2 \pm 0.77	77.0 - 83.2
Morococha	4,540	14,900	446.0	15	78.9 \pm 0.63	70.7 - 83.8
La Cima	4,835	15,860	433.8	7	75.3 \pm 0.93	70.4 - 79.8

* Determinations made within the first two hours after arrival

10 healthy men, also medical students, were taken from sea level to Morococha, at an altitude of 4,540 meters (14,900 feet), where 6 of them were investigated immediately after arrival from the point of view of possible changes in the total circulating blood volume and the remaining 4 were studied daily during a period of six days' residence at that altitude. In order to know the degree of anoxemia at which the hematologic observations were made, arterial blood was taken from several subjects at each one of the altitudes reached and analyzed for its oxygen saturation, the results obtained are given in table 7. The mean saturation ranged, from the lowest to the highest altitude, between 91.0 and 75.3 per cent. The results obtained in the different investigations have been summarized in table 8. In most cases there occurred a moderate rise in the red blood cells and hemoglobin, the average increases in the latter substance at the four altitudes, from the lowest to the highest, were 0.29, 0.13, 0.57 and 0.47 Gm per hundred cubic centimeters of blood, which represented increases of 1.8, 0.8, 3.6 and 2.9 per cent respectively, over the sea level value. There were marked individual variations (chart 2). In 11 of the subjects no change was found, this being more frequent at the lowest altitudes. In 15 men, 5 at the lower altitudes and 10 at the highest two, an actual decrease occurred, reaching a maximal value of 0.75 Gm in 1 subject studied at 3,140 meters, it was interesting to observe that in this group of 15 subjects were included 8 of the 12 men who engaged in physical activity after arrival at high altitudes. In the other 41 subjects, or 61 per cent of the total, the hemoglobin concentration rose under the influence of the acute anoxemia, the greatest increase was 1.70 Gm per hundred cubic centimeters, found in 2 men at the altitudes of 4,165

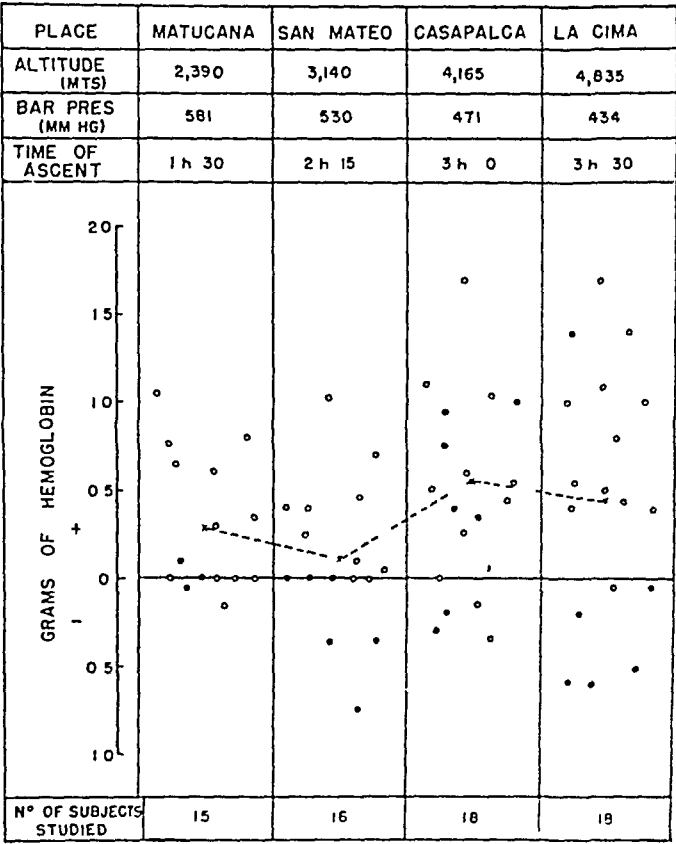


Chart 2—Variations in the blood hemoglobin (expressed in grams per hundred cubic centimeters) in 67 healthy men studied within the first three hours after their arrival at high altitudes. Dots represent men who engaged in physical activity (walking) previous to the taking of the blood sample, circles, resting men.

Of the 36 men studied on arrival at the altitudes of 4,165 and 4,835 meters, 13 showed at the time when the blood was taken signs and symptoms of *soroche* (mountain sickness). The occurrence of this syndrome did not have a definite relationship to the level of hemoglobin before the exposure, in the men with *soroche* the hemoglobin at sea level had an average value of

15 68 Gm per hundred cubic centimeters, as compared with 16 00 Gm in the unaffected group. However, of 6 subjects who before exposure had a hemoglobin concentration below 15 00 Gm, 4 showed symptoms on arrival at high altitudes. The average increase in hemoglobin in the ill men was 0 40 Gm per hundred cubic centimeters, and 5, or 38 5 per cent, showed a decrease at high altitudes. In the men without symptoms the

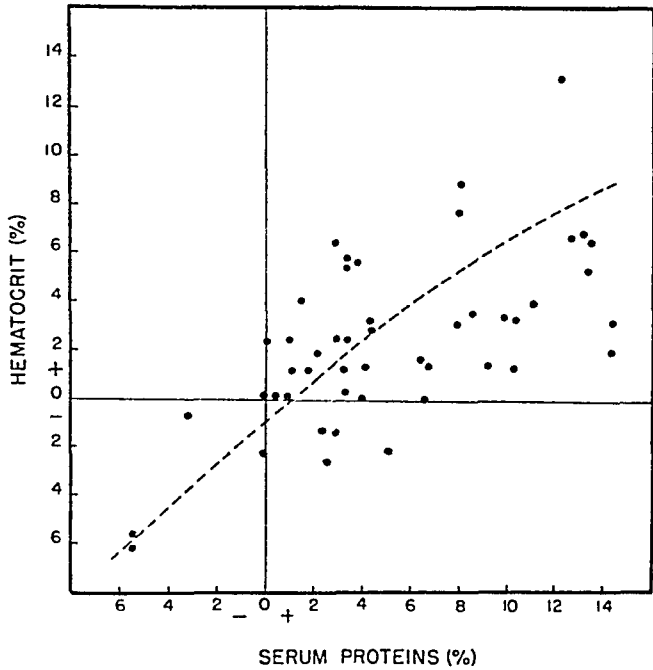


Chart 3—Relationship between the percentage increase of serum proteins and of hematocrit value for 48 healthy adult men studied within the first three hours after arrival at high altitudes (from 2,390 to 4,835 meters)

average increase observed was 0 53 Gm, and only 4, or 17 4 per cent, exhibited a decrease.

The concentration of serum proteins, determined for 50 of the subjects at sea level and after arrival at high altitudes, showed a definite rise, which had a direct relationship with the level of altitude. The average observed increases were 0 19, 0 32, 0 48 and 0 64 Gm per hundred cubic centimeters at the altitudes of 2,390, 3,140, 4,165 and 4,835 meters, respectively, which represented increases of 2 9, 4 0, 5 3 and 7 9 per cent over the sea level values. Some relationship was also observed between the degree of increase in the serum proteins and in the hematocrit value (cubic centimeters of red cells per hundred cubic centimeters of blood), but the rises in the latter (1 6, 1 5, 2 3 and 3 5 per cent, at the different altitudes, over the sea level values) were proportionately less than those observed in the protein substances (charts 3 and 4).

Although on arrival at high altitudes the men showed some individual changes in the morphologic characteristics of the red blood cells (mean corpuscular volume, hemoglobin and hemoglobin concentration), no definite trends

were observed, and the mean values were almost identical with those obtained previously at sea level (table 8).

The number of reticulocytes determined in thousands per cubic millimeter of blood showed a very slight rise at the high altitudes, a finding related to the increase in the number of red cells, the percentage values did not vary. The serum bilirubin did not show a constant change during the short exposure to the low barometric pressure, with the exception of a slight mean rise in the direct fraction at the highest altitude (4,835 meters).

With a variation of 2,000 or more white cells per cubic millimeter from the sea level value—taken as an arbitrary index of a significant change in the leukocyte count on a subject's arrival at a high altitude—we found a rise of this nature to occur in 5, 7 and 8 men at the altitudes of 3,140, 4,165 and 4,835 meters respectively (which corresponded to 31 2, 38 9, and 44 4 per cent of the subjects studied at these altitudes). In 6 of these subjects the increased count exceeded 10,000 per cubic millimeter, the highest value, 16,040 leukocytes, occurred in a subject studied at 4,165 meters (chart 5). In 2 men a significant

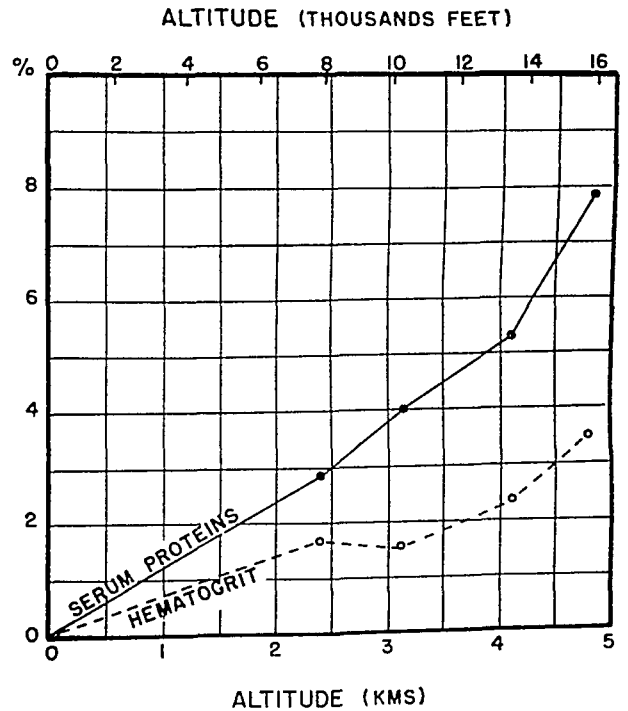


Chart 4—Mean percentage increase in serum proteins and hematocrit value within the first three hours after arrival at altitudes of 2,390, 3,140, 4,165 and 4,835 meters. Observations made on healthy adult men.

decrease was observed, and no change took place at the lowest altitude. Physical activity and *soroche* were frequently associated with a rise in the leukocyte count, in 4 of the 6 men who exercised at the highest stations and in 8 of the 13 patients with *soroche* this change was observed. The frequent rise in the number of

TABLE 8—Observations on Blood Made in Lima (at Sea Level) and Immediately After Arrival at Several Places of High Altitude* (Four Different Groups of Men Studied)

Place	Lima	Matucana	Lima	San Mateo	Lima	Casapalca	Lima	La Cima
Altitude (meters)	Sea level	2,390	Sea level	3,140	Sea level	4,165	Sea level	4,835
Number of subjects	15		16		18		18	
	Mean \pm P E							
Red blood cells (millions per cu mm)	4.96 \pm 0.06	4.97 \pm 0.04	5.11 \pm 0.06	5.14 \pm 0.05	4.88 \pm 0.05	5.05 \pm 0.04	5.01 \pm 0.04	5.17 \pm 0.05
Hematocrit (red cells, per cent)	45.7 \pm 0.13	46.5 \pm 0.50	46.3 \pm 0.31	46.8 \pm 0.31	45.7 \pm 0.36	46.9 \pm 0.43	45.8 \pm 0.24	47.7 \pm 0.35
Hemoglobin (Gm per 100 cc)	15.93 \pm 0.13	16.22 \pm 0.16	16.18 \pm 0.14	16.31 \pm 0.15	15.63 \pm 0.18	16.15 \pm 0.15	16.06 \pm 0.11	16.53 \pm 0.18
Corpuscular mean volume (cu microns)	92.0 \pm 0.79	93.1 \pm 0.50	90.8 \pm 0.89	91.2 \pm 0.57	93.7 \pm 0.77	93.0 \pm 1.28	91.3 \pm 0.71	92.0 \pm 0.51
Corpuscular mean Hb (micromicrograms)	32.2 \pm 0.32	32.7 \pm 0.29	31.7 \pm 0.28	31.8 \pm 0.17	32.2 \pm 0.30	32.3 \pm 0.46	32.0 \pm 0.30	31.8 \pm 0.27
Corpuscular mean Hb concentration (%)	34.8 \pm 0.18	34.9 \pm 0.16	35.0 \pm 0.21	34.8 \pm 0.19	34.5 \pm 0.28	34.7 \pm 0.19	35.0 \pm 0.16	34.6 \pm 0.16
Reticulocytes (per cent)	0.3 \pm 0.03	0.5 \pm 0.05	0.3 \pm 0.03	0.5 \pm 0.08	0.3 \pm 0.03	0.4 \pm 0.05	0.3 \pm 0.03	0.4 \pm 0.04
Reticulocytes (thousands per cu mm)	14.6 \pm 2.19	24.6 \pm 2.99	15.6 \pm 2.84	24.9 \pm 4.22	16.3 \pm 1.27	19.8 \pm 2.22	15.0 \pm 2.18	21.8 \pm 2.50
Serum proteins (Gm per 100 cc)	7.41 \pm 0.06	7.60 \pm 0.07	7.21 \pm 0.05	7.53 \pm 0.06	7.52 \pm 0.06	8.00 \pm 0.05	7.25 \pm 0.06	7.80 \pm 0.06
Bilirubin, direct (mg per 100 cc)	0.49 \pm 0.04	0.15 \pm 0.03	0.36 \pm 0.02	0.36 \pm 0.02	0.33 \pm 0.01	0.36 \pm 0.02	0.32 \pm 0.02	0.39 \pm 0.03
Bilirubin, indirect (mg per 100 cc)	0.31 \pm 0.02	0.31 \pm 0.02	0.28 \pm 0.03	0.31 \pm 0.03	0.38 \pm 0.02	0.38 \pm 0.03	0.38 \pm 0.03	0.40 \pm 0.04
Bilirubin, total (mg per 100 cc)	0.80 \pm 0.04	0.76 \pm 0.04	0.64 \pm 0.05	0.67 \pm 0.04	0.71 \pm 0.03	0.74 \pm 0.04	0.70 \pm 0.06	0.79 \pm 0.07
Leukocytes (thousands per cu mm)	6.98 \pm 0.17	6.84 \pm 0.17	7.05 \pm 0.23	7.73 \pm 0.26	6.94 \pm 0.21	8.24 \pm 0.41	6.28 \pm 0.17	8.40 \pm 0.29
Leukocyte differential count								
Neutrophils, stab (%)	25 \pm 20	18 \pm 24	16 \pm 24	21 \pm 36	24 \pm 19	18 \pm 16	29 \pm 29	28 \pm 39
Neutrophils, segmented (%)	55.8 \pm 1.35	57.3 \pm 1.87	54.3 \pm 1.55	61.9 \pm 1.72	53.9 \pm 1.21	57.1 \pm 1.81	54.1 \pm 0.99	62.0 \pm 1.91
Neutrophils, total (%)	58.3 \pm 1.51	59.1 \pm 1.94	55.9 \pm 1.55	64.0 \pm 1.77	56.3 \pm 1.19	58.7 \pm 1.65	57.0 \pm 1.03	61.8 \pm 2.00
Lymphocytes (%)	19 \pm 73	18 \pm 86	35 \pm 60	24 \pm 31	42 \pm 19	16 \pm 33	36 \pm 47	33 \pm 49
Monocytes (%)	0.6 \pm 0.09	0.4 \pm 0.09	0.6 \pm 0.09	0.8 \pm 0.11	0.5 \pm 0.09	0.5 \pm 0.09	0.8 \pm 0.10	0.6 \pm 0.15
Eosinophils (%)	0.9 \pm 0.18	5.4 \pm 0.26	0.9 \pm 0.44	4.8 \pm 0.35	7.1 \pm 0.41	6.8 \pm 0.47	7.2 \pm 0.50	3.1 \pm 0.47
Lymphocytes (%)	29.3 \pm 0.95	30.3 \pm 1.61	33.1 \pm 1.21	28.0 \pm 1.42	32.2 \pm 0.99	30.0 \pm 1.43	31.3 \pm 0.56	28.3 \pm 1.41

* The time of ascent from sea level to the different altitudes was as follows: Lima to Matucana, 1 hour, 30 minutes; Lima to San Mateo, 2 hours, 15 minutes; Lima to Casapalca, 3 hours; Lima to La Cima 3 hours 30 minutes.

leukocytes on the subjects' arrival at high altitudes was almost entirely due to an increase in the segmented neutrophils, the monocytes and the lymphocytes showed a proportional decrease. No constant changes were observed in the number of stab neutrophils, eosinophils and basophils. The occurrence of a temporary leukocytosis under the influence of a low pressure environment has been already reported. Meyer, Seevers and Beatty,⁴¹ working with rats, and Sokolov⁴² experimenting with cold-blooded animals, have observed such a hematic response in experiments carried out in chambers.

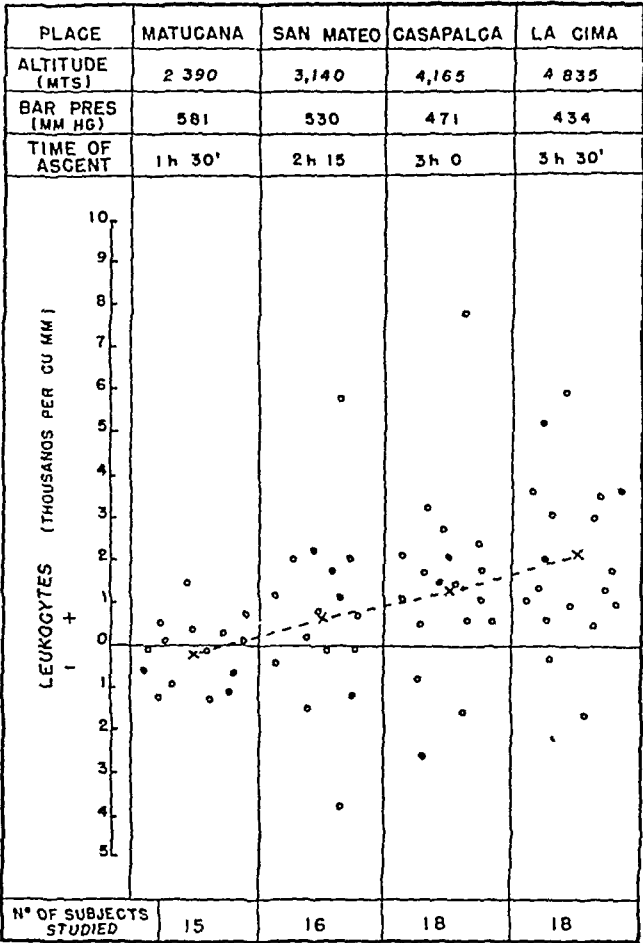


Chart 5—Variation in the leukocyte counts (expressed in thousands per cubic millimeter) of 67 healthy men studied within three hours after arrival at high altitudes. Dots represent men who engaged in physical activity (walking) previous to the taking of the blood sample, circles, resting men.

In order to study further the mechanisms which are related to the polycythemic response to a condition of acute anoxemia we made determinations of blood volume for 6 subjects (medical students) within the first two hours after their arrival at Morococha, at an altitude of 4,540 meters (14,900 feet). Previous determinations had been made at sea level a few days before the

ascent. The results obtained are given in table 9 and presented, graphically, in chart 6. The plasma volume remained unchanged in 2 subjects and decreased in the other 4, the average reduction in volume was 0.26 liters, equivalent to 10.5 per cent. The red cell volume increased in 5 subjects, and the elevation averaged 0.32 liters, or 13.8 per cent. In 3 of the men the total serum proteins rose on arrival at high altitudes, the increase had an average value of 10 Gm, equal to 8.2 per cent. In 1 subject a decrease of 13 Gm (7.9 per cent) was found, and in the other 2 no significant change was verified.

The subsequent changes which take place in the circulating blood when the anoxic stimulus is prolonged for a few days were studied in a group of 4 men (medical students of ages varying between 21 and 25 years) who were taken from sea level to Morococha (at an altitude of 4,540 meters [14,900 feet]), where they remained for six days. The various investigations made previously at sea level were repeated on their arrival and then daily during the time of their residence at high altitudes. Determinations of blood volume were also made. The findings are given in tables 10 and 11. The moderate increase in the red blood cells and hemoglobin observed on the men's arrival was followed by a gradual rise, while the serum proteins, found to be sharply elevated in the first observation made at high altitudes, remained about unchanged, with a slight tendency to decrease (chart 7). One day after the men arrived the reticulocytes began to show an increase, which in the sixth, and last, day of study reached values of 2.2 to 4.0 per cent. This finding indicated a definite response of the bone marrow to the anoxic stimulus. In 3 subjects there was a moderate decrease in the mean corpuscular volume, while the mean corpuscular hemoglobin concentration remained practically unchanged. The plasma bilirubin, directly and indirectly determined, and total amount, did not show a significant variation except in 1 subject, who at sea level, before the ascent, had an abnormally high concentration of pigment. This subject three days after arrival at high altitudes had a considerable rise in the directly and indirectly determined bilirubin, with a subsequent decrease but without a decline to the initial value. It was interesting to observe in all subjects twenty-four hours after arrival a temporary and moderate rise in the leukocytes (chart 8) which was simultaneous with the beginning of the hyperactivity of the bone marrow as shown by the rise of the reticulocytes. The increase was almost entirely due to an elevated number of segmented neutrophils, there was no change in the stab neutrophils. The determinations of blood volume made after two, four and six days of residence

41 Meyer, O. O., Seevers, M. H., and Beatty, S. R. *Am J Physiol* **113** 166, 1935.
42 Sokolov, A. N. *J Med, Kiev* **11** 145, 1941.

at high altitudes (chart 6) showed, in comparison with the values obtained at sea level, an unchanged plasma volume in 3 subjects, an increased volume in 1 (137 per cent) and a decreased volume in another (10.9 per cent). The cell volume was elevated in all subjects (120

Our observations concerning the changes which take place in the circulating blood volume during a short period of residence at high altitudes are not strictly comparable with those made by Smith, Belt, Arnold and Carrier⁴³ at an altitude of 3,350 meters. These investigators found

TABLE 9—*Determinations of Blood Volume Made at Sea Level and Within the First Two Hours After Arrival at Morococha (at 4,540 meters, 14,900 feet) **

Sub jects	Blood Volume			Plasma Volume			Red Cell Volume			Total Hemoglobin			Total Serum Protein		
	Liters		Vari- ation, %	Liters		Vari- ation, %	Liters		Vari- ation, %	Grams		Vari- ation, %	Grams		Vari- ation, %
	Sea Level	Moro cocha		Sea Level	Moro cocha		Sea Level	Moro- cocha		Sea Level	Moro cocha		Sea Level	Moro cocha	
1	4.28	3.92	-8.4	2.35	1.95	-17.0	1.91	1.95	+2.1	685	663	-2.5	165	152	-7.9
2	4.24	4.53	+6.8	2.36	2.15	-8.9	1.86	2.35	+20.8	670	743	+10.9	169	171	+1.2
3	4.49	4.76	+6.0	2.49	2.52	+1.2	1.98	2.22	+10.8	678	752	+10.9	178	193	+8.4
4	4.71	5.16	+9.6	2.30	2.35	+2.2	2.39	2.79	+16.7	782	893	+14.2	162	180	+11.1
5	5.19	5.24	+1.0	2.85	2.65	-7.0	2.31	2.56	+12.8	781	859	+10.0	185	186	+0.4
6	4.61	4.78	-0.6	2.70	2.46	-8.9	2.09	2.30	+10.0	721	784	+8.7	181	190	+5.0

* Average time of ascent, 3 hours

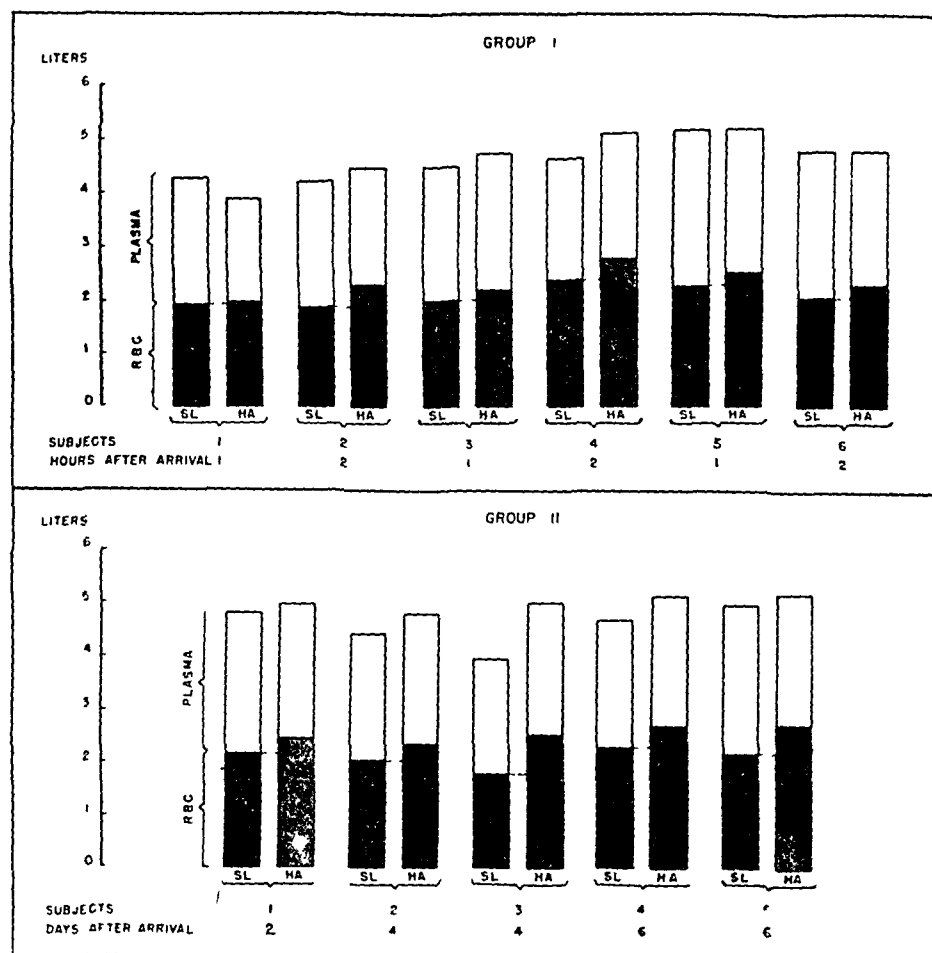


Chart 6—Results of determinations of blood volume made for 11 healthy adult men at sea level and repeated at high altitudes (at 4,540 meters, 14,900 feet). Group I, determinations made one to two hours after their arrival. Group II, determinations made a few days after their arrival. The black zone represents red cell volume, the white zone, plasma volume.

to 43.4 per cent), and the total serum proteins showed increases in all of them (4.3 to 28.0 per cent). Increases, which fluctuated between 133 and 243 Gm, were found in the total amount of circulating hemoglobin. As a whole, all these changes had some proportional relationship to the length of residence at high altitudes.

no abrupt changes within the first day or two at that altitude, after two or three weeks an average increase of 19 per cent in the red cell volume was verified, the plasma volume did not show any significant variation. In 1913 Douglas,

43 Smith, H. P., Belt, A. E., Arnold, H. R., and Carrier, E. B. *Am. J. Physiol.* 71:305, 1925.

Haldane, Henderson and Schneider,⁴⁴ working at Pike's Peak, Colorado, at an altitude of 4,300 meters, and employing the carbon monoxide method, observed a significant rise in the blood

those experienced by pilots and other flight personnel, has attained a considerable interest in the last few years. Attention has been given to the psychologic aspects as well as to the adaptive responses of the respiratory and circulatory systems. Few investigations have been made concerning the morphologic response of the blood. Meyer and Seyderhelm,⁴⁶ in 1916, studied the blood of 28 men who had been engaged in flying for a year or more and found in all cases an increase in the red blood cells and hemoglobin. McFarland, Graybiel, Liljencrantz and Tuttle,⁴⁷ in an analysis of the data collected in the examination of 200 civil air line pilots, the vast majority of whom had a record of flying at altitudes not over 3,050 meters (10,000 feet), found a red cell count above 6,000,000 in 50 per cent of them, the hemoglobin did not show a parallel

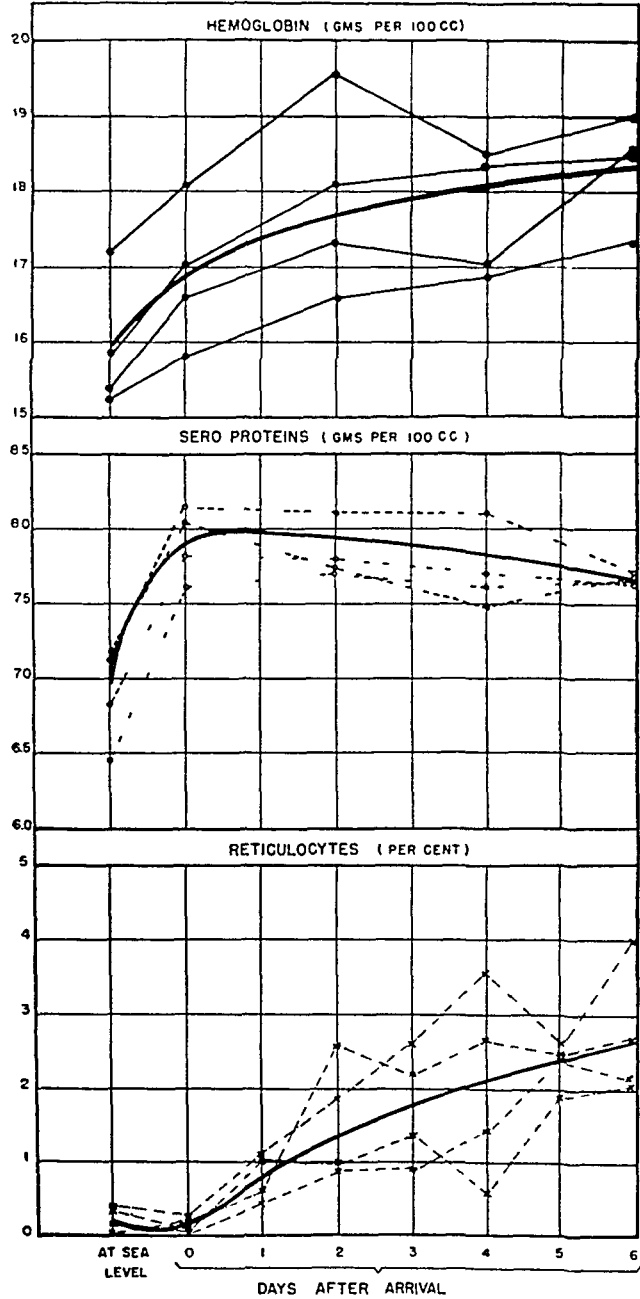


Chart 7—Values for hemoglobin, serum proteins and reticulocytes in 4 healthy men studied at sea level and during six days of residence at an altitude of 4,540 meters (14,900 feet). The heavy lines represent the average values.

volume of 3 of the 4 subjects after a residence of nine to ten days. Laquer⁴⁵ found an increase of 5 per cent in the blood volume after four weeks of residence at an elevation of 1,560 meters.

INFLUENCE OF INTERMITTENT ANOXEMIA

The study of the effects produced on the body by intermittent periods of anoxemia, such as

44 Douglas, C. G., Haldane, J. S., Henderson, Y., and Schneider, E. C. *Philos. Tr. Roy. Soc., London*, s. B. **203**, 185, 1913.
45 Laquer, F. *Klin. Wchnschr.* **3**, 7, 1924.

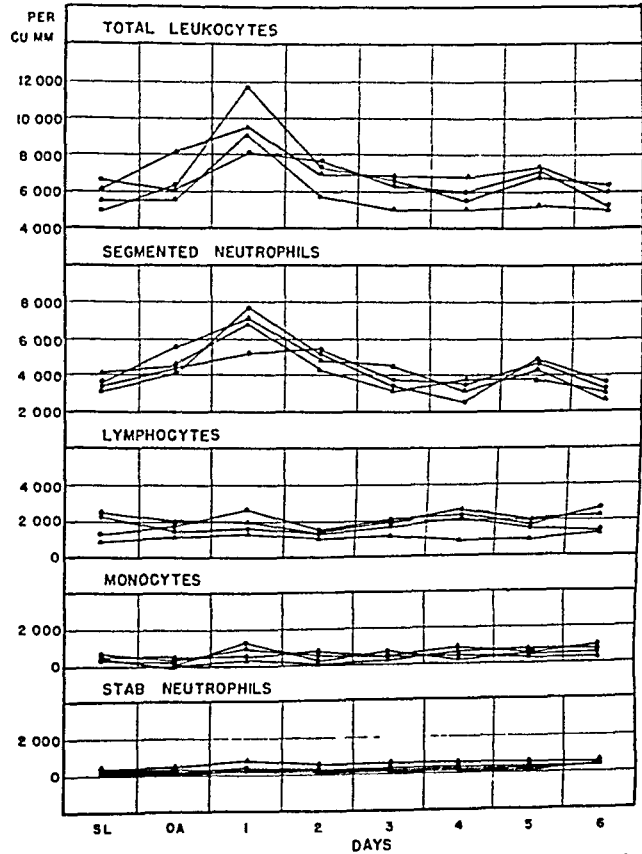


Chart 8—Leukocyte counts for 4 healthy men studied at sea level and immediately after arrival and during a residence of six days at an altitude of 4,540 meters (14,900 feet). The rise observed twenty-four hours after their arrival corresponded to the beginning of the reticulocytosis (chart 7).

increase. Armstrong⁴⁸ and Heim observed that exposure for a period of four hours for three consecutive days to a simulated altitude of 3,660

46 Meyer, E., and Seyderhelm, R. *Deutsche med. Wchnschr.* **42**, 1245, 1916.
47 McFarland, R. A., Graybiel, A., Liljencrantz, E., and Tuttle, A. D. *J. Aviation Med.* **10**, 160, 1939.
48 Armstrong, H. G. *Principles and Practice of Aviation Medicine*, Baltimore, Williams & Wilkins Company, 1939.

TABLE 10—Observations on Blood of Four Men During a Six Day Residence in Morococha (4,540 Meters 14,900 Feet)

Observations	Subject 1									Subject 2								
	At S L* O A†		Days at High Altitudes						At S L* O A†		Days at High Altitudes							
			1	2	3	4	5	6			1	2	3	4	5	6		
Red blood cells (mill per cu mm)	4 99	4 99	5 53	5 71	5 57	5 63	5 28	5 45	4 78	4 62	5 11	5 48	5 03	4 88	4 95	4 99		
Hemoglobin (Gm per 100 cc)	15 4	16 6		17 3		17 1		18 6	15 3	15 8		16 6		16 8		17		
Hematocrit (red cells, per cent)	46 4	46 8		49 6		49 0		51 5	44 2	45 7		48 8		50 0		49 1		
Reticulocytes (per cent)	0 4	0	0 4	1 0	0 8	1 4	2 4	2 2	0 4	0	1 2	0 8	1 4	0 6	1 8	2 2		
Reticulocytes (thous per cu mm)	20 0	0	22 1	57 1	44 6	18 8	126 7	120 0	19 1	0	61 3	43 8	70 4	29 3	89 1	169 1		
Bilirubin, total (mg per 100 cc)	0 66	0 57		0 63		0 77		0 72	0 90	0 72		0 63		0 70		0 57		
Bilirubin, direct (mg per 100 cc)	0 40	0 37		0 45		0 47		0 33	0 50	0 45		0 49		0 52		0 55		
Bilirubin, indirect (mg per 100 cc)	0 26	0 20		0 23		0 30		0 39	0 40	0 27		0 14		0 18		0 22		
Leukocytes (thous per cu mm)	6 63	6 08	8 08	7 72	6 40	6 00	7 16	5 28	5 00	6 16	11 8	7 56	6 44	5 69	7 08	6 14		
Serum protein (Gm per 100 cc)	7 14	8 08		7 76		7 47		7 72	6 83	7 88		7 74		7 72		7 18		
	Subject 3									Subject 4								
	At S L* O A†		Days at High Altitudes						At S L* O A†		Days at High Altitudes							
			1	2	3	4	5	6			1	2	3	4	5	6		
Red blood cells (mill per cu mm)	5 25	5 74	5 84	5 80	6 11	6 32	5 80	6 49	4 91	5 35	5 78	5 58	6 25	5 72	5 89	6 25		
Hemoglobin (Gm per 100 cc)	17 2	18 1		19 6		18 5		19 0	15 9	17 1		18 1		18 4		18 5		
Hematocrit (red cells, per cent)	49 2	50 7		53 4		53 9		52 8	43 9	45 7		50 7		49 2		52 0		
Reticulocytes (per cent)	0	0 2	1 2	1 8	2 6	3 6	2 6	4 0	0 2	0 2	0 6	2 6	2 2	2 6	2 4	2 6		
Reticulocytes (thous per cu mm)	0	11 5	70 1	104 4	158 9	227 5	150 8	259 6	9 8	10 7	34 7	145 1	137 5	148 7	141 4	167 5		
Bilirubin, total (mg per 100 cc)	1 03	0 68		0 97		0 88		0 72	1 34	1 52		2 56		1 90		1 90		
Bilirubin, direct (mg per 100 cc)	0 45	0 30		0 37		0 54		0 33	0 47	0 68		1 14		0 85		0 85		
Bilirubin, indirect (mg per 100 cc)	0 58	0 38		0 60		0 34		0 39	0 87	0 84		1 42		1 05		1 05		
Leukocytes (thous per cu mm)	5 60	5 64	9 04	5 88	5 12	5 08	5 16	5 01	6 24	8 10	9 60	7 63	6 96	6 96	7 08	6 16		
Serum protein (Gm per 100 cc)	7 19	8 14		8 12		8 12		7 66	6 45	7 62		7 72		7 61		7 63		

* At S L = at sea level
† O A = on arrival at high altitude

TABLE 11—Determinations of Blood Volume at Sea Level and After a Few Days of Residence in Morococha (at 4,540 meters, 14,900 feet)

Sub jects	Days in Moro cocha	Blood Volume			Plasma Volume			Red Cell Volume			Total Hemoglobin			Total Serum Protein		
		Liters		Varia tion, %	Liters		Varia tion, %	Liters		Varia tion, %	Grams		Varia tion, %	Grams		Varia tion, %
		Sea Level	Moro cocha		Sea Level	Moro cocha		Sea Level	Moro cocha		Sea Level	Moro cocha		Sea Level	Moro cocha	
1	2	4 80	4 97	+ 3 5	2 60	2 51	— 3 5	2 17	2 43	+12 0	737	870	+18 0	185	193	+ 4 3
2	4	4 42	4 81	+ 8 8	2 35	2 43	+ 3 3	2 05	2 36	+15 1	678	820	+20 9	163	182	+ 8 3
3	4	3 96	5 03	+27 0	2 19	2 49	+13 7	1 75	2 51	+43 4	604	847	+40 2	150	192	+28 0
4	6	4 67	5 16	+10 5	2 35	2 41	+ 2 5	2 30	2 72	+18 2	803	950	+22 0	169	185	+ 9 5
5	6	4 96	5 18	+ 4 4	2 76	2 46	—10 9	2 18	2 69	+23 4	786	953	+21 9	178	189	+ 6 2

TABLE 12—Observations on Blood of Flight Personnel

	Number of Subjects	Mean ± P E		St Dev ± P E	Coefficient of Varia tion, %	Extreme Variation
Red blood cells (millions per cu mm)	60	5 02	± 0 04	0 51	± 0 03	3 78 6 25
Hematocrit (red cells, per cent)	60	47 4	± 0 25	2 9	± 0 18	38 1 53 0
Hemoglobin (Gm per 100 cc)	60	16 53	± 0 09	1 11	± 0 07	14 10 19 10
Corpuscular mean volume (cu microns)	60	94 3	± 0 56	6 4	± 0 39	77 5 107 4
Corpuscular mean hemoglobin (micromicrograms)	60	33 0	± 0 18	2 1	± 0 13	27 2 37 3
Corpuscular mean hemoglobin concentration (%)	60	35 1	± 0 18	2 1	± 0 13	31 9 37 9
Reticulocytes (per cent)	60	0 7	± 0 05	0 6	± 0 03	0 3 9
Reticulocytes (thousands per cu mm)	60	35 7	± 2 63	30 2	± 1 56	0 161 4
Bilirubin, total (mg per 100 cc)	45	1 00	± 0 06	0 63	± 0 04	0 35 3 43
Bilirubin, direct (mg per 100 cc)	45	0 43	± 0 02	0 18	± 0 01	0 12 1 05
Bilirubin, indirect (mg per 100 cc)	45	0 56	± 0 05	0 35	± 0 04	0 10 2 67
Leukocytes (per cu mm)	60	6,450	± 137	1,550	± 97	3,400 11,100
Leukocytic differential count	45					
Neutrophils, stab (per cent)		4 0	± 0 21	2 1	± 0 15	0 9
Neutrophils, segmented (per cent)		56 8	± 0 73	7 9	± 0 56	6 7
Neutrophils, total (per cent)		60 6	± 0 82	8 2	± 0 53	41 50
Eosinophils (per cent)		3 6	± 0 23	2 3	± 0 16	0 9
Basophils (per cent)		0 4	± 0 03	0 6	± 0 04	0 7
Monocytes (per cent)		6 0	± 0 33	3 3	± 0 23	0 14 7
Lymphocytes (per cent)		26 6	± 0 78	7 5	± 0 55	24 1

meters (12,000 feet) resulted in a decrease of the hemoglobin and the red cell count. Frequent exposures to carbon monoxide, which causes anoxemia by displacement of the oxygen from the circulating hemoglobin, at the same time decreasing the affinity of this substance for the latter gas,⁴⁹ has been found to produce a polycythemic response.⁵⁰ In a recent investigation, Stickney and Van Liere⁵¹ observed a rise in the red blood cells and hemoglobin in dogs exposed six to nine hours daily for six months to simulated altitudes between 3,660 meters (12,000

Our studies include observations made on two groups of healthy men, both subject to the influence of intermittent periods of anoxemia but different from each other in regard to the length of time of exposure.

Observations on Flight Personnel—Hematologic studies were carried out for 60 men, members of the flight personnel of a commercial air line which operates in South America, 47 of these men were pilots or co-pilots, 10 radio operators and 3 pursers. Fifty-seven had been born in the United States and 3 in Peru. Their ages varied between 21 and 49 years, with an average of 29 years. The total flying time of each man fluctuated between two hundred and several thousand hours, with a monthly average of sixty to ninety hours. Some of the routes covered by this air line require flying for several hours at altitudes over 3,660 meters (12,000 feet), most of the men reported the use of oxygen while flying over that level. The examinations were made from one to fourteen days after the previous trip. The results obtained are given in table 12.

The mean values of the hemoglobin content (grams per hundred cubic centimeters) and the hematocrit reading (percentage of red cells) were slightly higher than those obtained for the group of healthy men not subject to the influence of a low barometric pressure. Study of the individual findings (chart 9) revealed that 14 (23.3 per cent) of the 60 men had a hemoglobin concentration of 17.5 Gm or more, the highest observed value was 19.10 Gm. Twelve men (20 per cent) had hematocrit values of 50 per cent or more, the highest being 53. Two subjects (3.3 per cent of the total) were found to have hemoglobin values of 14.1 and 14.5 Gm per hundred cubic centimeters, with corresponding hematocrit readings of 38.1 and 40.4 per cent red cells, these values were the lowest found in this series of investigations. There was no correlation between the blood findings and the time spent at sea level after the previous trip, the latter had a similar average value of six days for the groups of men with hemoglobin concentrations above and below 17 Gm.

The mean corpuscular volume, of 94.3 ± 0.56 cubic microns, of the flight personnel was slightly higher than the corresponding value (91.3 ± 0.23) for the control group studied at sea level, in 12 cases (20 per cent) the volume exceeded 100 cubic microns. The mean corpuscular hemoglobin concentration ranged within normal limits. The reticulocytes, expressed in percentage and in number per cubic millimeter, had higher mean values in the group of fliers, 15 (25 per cent) of the 60 men studied had one or more red blood cells per hundred that appeared to be reticulated.

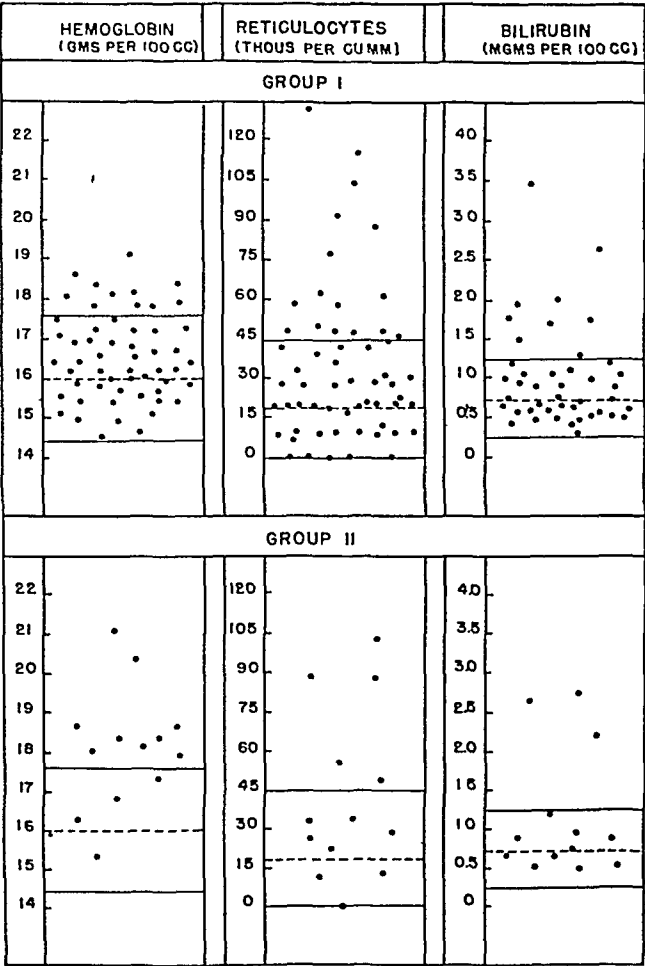


Chart 9—Values for hemoglobin, reticulocytes and bilirubin in men exposed to intermittent periods of anoxemia. Group I, flight personnel, group II, railroad personnel (see text). The zones between the horizontal lines show the limits of variation observed in healthy men at sea level.

feet) and 4,880 meters (16,000 feet), these investigators concluded that discontinuous exposure to anoxia is capable of producing a noticeable acclimatization, the degree of which, in terms of increase in hemoglobin and erythrocytes, is proportional to the severity of the anoxia and the length of time of exposure.

49 Haldane, J. S., and Priestley, J. G. *Respiration*, London, Oxford University Press, 1935.
50 Killick, E. M. *Physiol Rev* 20:313, 1940.
51 Stickney, J. C., and Van Liere, E. J. *J. Aviation Med* 13:170, 1942.

The serum bilirubin, determined for 45 men of the flight personnel, showed significant variations. The mean values, of 0.43 ± 0.02 , 0.56 ± 0.05 and 1.00 ± 0.06 mg per hundred cubic centimeters, for the directly and indirectly determined and total bilirubin, respectively, were higher than the corresponding values found in the blood of the subjects we studied for comparative purposes. The increase was more marked in the indirect (51.3 per cent) than in the direct value (22.8 per cent), this lowered the ratio direct/total bilirubin, which in the flight personnel had an average value of 43 per cent, as compared with 51.4 per cent in the nonfliers. Seventeen of the 45 men studied, or 37.8 per cent, had a total bilirubin content of over 1 mg, while this was found in only 13 per cent of the

spent alternate nights at sea level and at an altitude of 3,730 meters (12,340 feet), traveling daily for several hours, one day on ascent and the next on descent, without taking oxygen, along a road whose highest point is at an altitude of 4,740 meters (15,510 feet). Observations were made on 13 of these men during one of the brief periods they were in Lima, at sea level, their ages varied between 23 and 54 years. Ten had been born at high altitudes and 3 at sea level. The time during which they had been intermittently exposed to a low barometric pressure, with the exception of one month's vacation each year, fluctuated between one and twenty-eight years. The results found in the different investigations, which included determinations of blood volume for 11 of the men, are given in tables 13 and 14.

TABLE 13—Observations on Blood of Men Daily Exposed to a Low Barometric Pressure (Railroad Personnel)

Subjects	Age, Years	Years of Exposure	Red Blood Cells, Millions per Cu Mm	Hematocrit, Red Blood Cells, per Cent	Hemoglobin, Gm per 100 Cc	Mean Corpuscular Volume, Cu Microns	Mean Corpuscular Hemoglobin, Micrograms	Mean Corpuscular Hemoglobin Concentration, per Cent	Reticulocytes		Bilirubin, Mg per 100 Cc		
									Per Cent	Thousands per Cu Mm	Total	Direct	Indirect
1	44	28	5.61	51.4	18.60	91.6	33.1	36.1	1.6	89.8	0.86	0.45	0.41
2	54	25	6.25	58.6	20.35	90.6	32.6	36.0	1.4	87.5	0.83	0.33	0.55
3	42	20	6.49	60.6	21.10	93.4	32.5	34.8	0.4	26.0	2.74	0.86	1.88
4	48	20	5.15	51.6	18.00	100.2	34.9	34.8	1.0	51.5	0.63	0.33	0.35
5	49	13	5.40	48.6	17.30	90.0	32.0	35.5	0.4	21.6	0.52	0.23	0.29
6	41	12	4.81	47.0	16.25	97.7	33.8	34.6	0.6	23.9	0.50	0.36	0.24
7	36	9	5.33	50.7	18.60	95.1	34.8	36.6	0.6	32.0	1.20	0.36	0.84
8	36	7	4.63	50.6	16.75	103.1	35.8	33.1	1.2	56.2	0.75	0.33	0.42
9	40	4	5.14	53.2	18.10	103.5	35.2	34.0	2.0	102.8	0.50	0.23	0.22
10	38	3	5.53	52.3	17.90	91.6	32.4	34.2	0.2	11.1	2.19	0.50	1.69
11	23	3	5.74	52.8	18.35	92.0	32.0	34.8	0.2	11.5	0.66	0.32	0.34
12	39	1	4.63	44.1	15.30	94.2	32.7	34.7	0	0	0.93	0.47	0.46
13	22	1	5.63	54.1	18.30	96.1	32.5	33.8	0.6	33.8	2.66	0.43	2.23
Mean \pm P E			5.42 ± 0.10	51.8 ± 0.76	18.07 ± 0.28	95.9 ± 0.99	33.4 ± 0.25	34.8 ± 0.18	0.8 ± 0.11	42.5 ± 6.16	1.16 ± 0.15	0.40 ± 0.03	0.76 ± 0.13
St Dev \pm P E			0.63 ± 0.07	3.9 ± 0.54	1.47 ± 0.20	5.1 ± 0.62	1.3 ± 0.17	0.9 ± 0.12	0.6 ± 0.06	31.6 ± 4.26	0.78 ± 0.10	0.15 ± 0.02	0.67 ± 0.09
Coefficient of variation, %			9.8	7.5	8.1	5.3	3.9	2.6	75.0	74.4	67.2	37.5	83.1

group studied at sea level, the high bilirubin values of 11 of the 17 subjects corresponded to an elevation in the indirectly determined pigment, and in the other 6 the directly determined bilirubin was responsible for the rise, though in a lesser degree.

The numbers of leukocytes per cubic millimeter and the differential leukocyte counts of the flight personnel did not show any significant variation when compared with the results obtained in the study of the men living constantly at sea level.

Observations on Men Daily Exposed to a Low Barometric Pressure—We had the opportunity to study a small group of men who occupied a perhaps unique position in regard to an intermittent exposure to a low barometric pressure. These men were members of the crew personnel of a railroad which connects Lima, at sea level with high localities on the Andean plateau (chart 1), and for a prolonged time they had

A rise in the hemoglobin content and in the hematocrit readings was frequently observed, the mean values, of 18.07 ± 0.28 Gm per hundred cubic centimeters and 51.8 ± 0.76 per cent red cells, respectively, were distinctly higher than those obtained for healthy males living constantly at sea level. The hemoglobin concentrations of 9 of the men (69.2 per cent) exceeded 17.50 Gm, and those of 2 of them reached the figures of 20.35 and 21.10 Gm (chart 9). The hematocrit readings of 10 of the subjects (76.9 per cent) was over 50.0 per cent, the highest observed value was 60.6 per cent. There was not a constant direct relationship between the time of exposure to the high altitude and the degree of polycythemia, however the three highest hemoglobin values, 18.60, 20.35 and 21.10 Gm per hundred cubic centimeters were found in the men who had the most prolonged time of service in the railroad, twenty-eight, twenty-five and twenty years, respectively.

The mean corpuscular volume, of 95.9 ± 0.99 cubic microns, was slightly higher than the one obtained for the group of men studied at sea level. The mean corpuscular hemoglobin concentration ranged within normal limits. The reticulocytes, in per cent and per cubic millimeter, also showed higher mean values than in men not exposed to high altitudes, in 5 cases (38.5 per cent) the percentage value fluctuated between 1.0 and 2.0. The plasma bilirubin was found to exceed 1.00 mg per hundred cubic centimeters in 5 of the men (38.5 per cent), this rise was due exclusively to a higher amount of the indirectly determined pigment, which had a mean increase of 117.1 per cent over the corresponding normal value at sea level. The ratio direct/total bilirubin had an average value of 34.5 per cent.

The number of leukocytes per cubic millimeter had a normal mean value, in only 1 case it was

showed an average increase of 22.7 per cent and was found to be elevated in 9 of the 11 men studied (81.8 per cent).

Five men had a history of occasionally having mild headache and a sensation of dizziness while traveling at high altitudes. When the data for these men were compared with those for the rest of the subjects, no significant variations were found to exist in the blood volume and other hematologic characteristics, except that 1 of the complaining men had the highest values for the hemoglobin content and the hematocrit reading (21.10 Gm and 60.6 per cent red cells, respectively).

INFLUENCE OF CHRONIC ANOXEMIA

Since the original observations of Bert,¹ Viault² and Muntz,⁵² in the second half of the last century, numerous investigations have con-

TABLE 14—Observations on Blood of Men Daily Exposed to a Low Barometric Pressure (Railroad Personnel)

Sub jects	Age, Years	Years of Expo sure	Leuko cytes, per Cu Mm	Leukocytic Differential Count, %							Blood Volume, Cc Gm per Kg			
				Stab Neutro phils	Segmented Neutro phils	Total Neutro phils	Eosino phils	Baso phils	Mono cytes	Lympho cytes	Blood	Plasma	Red Blood Cells	Hemo globin
1	44	28	6,800	5	56	61	5	0	4	30	82.3	39.6	42.3	15.3
2	54	25	11,900	3	71	74	0	1	3	22	93.8	40.3	53.0	19.1
3	42	20	6,880	9	57	66	1	0	8	25	78.0	30.4	47.3	16.5
4	48	20	4,600	3	78	81	0	4	4	11	102.2	48.9	52.7	18.4
5	49	13	5,000								76.6	39.0	37.2	13.2
6	41	12	7,600	1	60	61	4	0	1	34				
7	36	9	6,720	8	65.5	73.5	2.5	1	5.5	17.5	89.9	43.9	45.7	16.5
8	36	7	5,120	6	65	71	3.5	0	7.5	18	99.6	48.6	50.3	16.7
9	40	4	7,800	4	56	60	2	0	2	36				
10	38	3	6,060	4	46	50	2.5	0	7.5	40	98.2	46.3	51.3	17.6
11	23	3	8,700	4	52	56	2	0	5	37	86.8	40.6	45.8	15.6
12	39	1	6,600	2	60	62	3	0	2	33	87.3	48.4	38.6	13.4
13	22	1	5,920	5	65	70	2.5	1	6	20.5	87.5	39.5	47.0	15.9
Mean \pm P E			6,900 \pm 356	4.5 \pm 0.44	60.9 \pm 1.67	65.4 \pm 1.69	2.3 \pm 0.28	0.6 \pm 0.22	4.6 \pm 0.44	27.0 \pm 1.79	89.2 \pm 1.81	42.3 \pm 1.18	46.5 \pm 1.14	16.2 \pm 0.38
St Dev P E			1,830 \pm 252	2.2 \pm 0.31	8.2 \pm 1.18	8.3 \pm 1.19	1.4 \pm 0.20	1.1 \pm 0.15	2.2 \pm 0.32	8.8 \pm 1.26	8.1 \pm 1.22	5.3 \pm 0.79	5.1 \pm 0.76	1.7 \pm 0.25
Coef of variation, %			26.5	48.8	13.5	12.7	60.9	183.3	47.8	32.6	9.1	12.5	11.0	10.5

moderately elevated (11,900). The differential leukocyte count, made for 12 of the subjects, revealed a frequent and moderate increase in the segmented neutrophils with a corresponding decrease in the monocytes and lymphocytes, a change almost identical to the one found in men exposed to a temporary period of anoxemia (table 8).

The determinations of blood volume, made for 11 of the men, showed well defined changes (chart 10). The red cell volume, expressed in cubic centimeters per kilogram of body weight, was elevated in 7 of the men (63.6 per cent), its mean value, of 46.5 ± 1.14 cc, represented an increase of almost 20 per cent over the corresponding normal value at sea level. The plasma volume, expressed similarly, was decreased in 4 and unchanged in 7 subjects, its mean value was 10.2 per cent lower than in men not exposed to a low barometric pressure. The circulating hemoglobin, in grams per kilogram of body weight,

firmed the existence of polycythemia in human beings and animals living at high altitudes. The review of the literature,⁵³ a summary of which

52 Muntz, A. Compt rend Acad d sc **112** 298, 1891.
53 (a) Fitzgerald, M. P. Philos Tr Roy Soc, London, s B **203** 351, 1913. (b) Eggers, H. Munchen med Wchnschr **73** 779, 1926. (c) Monge, C., Heraud, C., Encinas, E., and Hurtado, A. Estudios fisiologicos sobre el hombre de los Andes, Lima, Facultad de Medicina, 1928. (d) Hurtado, A., and Guzman Barron, A. Rev med peruana, Lima **1** 1, 1930. (e) Hurtado, A. Am J Physiol **100** 487, 1932. (f) Stammers, A. D. J Physiol **78** 21P, 1933. (g) Liknaitzky, I. Quart J Exper Physiol **24** 161, 1934. (h) Talbott, J. H., and Dill, D. B. Am J M Sc **192** 626, 1936. (i) Andresen, M. I., and Mugrage, E. R. Blood Cell Values for Normal Men and Women, Arch Int Med **58** 136 (July) 1936. (j) Loewy, A., and Wittkower, E. The Pathology of High Altitude, London, Oxford University Press, 1937. (k) Capdehourat, E. L., and others. Estudios sobre la biología del hombre de la altitud, Buenos Aires, Ministerio de Justicia e Instruccion Publica, 1937. (l) Barcroft and others.³

is given in table 15, indicates, however, a marked variability in the degree and other characteristics of the observed polycythemia, it is likely that this is related, at least in part, to the variable factors of altitude and the duration of exposure. We have made observations on three groups of men

mines and in whom the degree of anoxemia was frequently abnormally accentuated owing to the pulmonary changes, and (c) men, also of Indian race, who had signs of loss of adaptation to the low pressure environment (chronic mountain sickness)

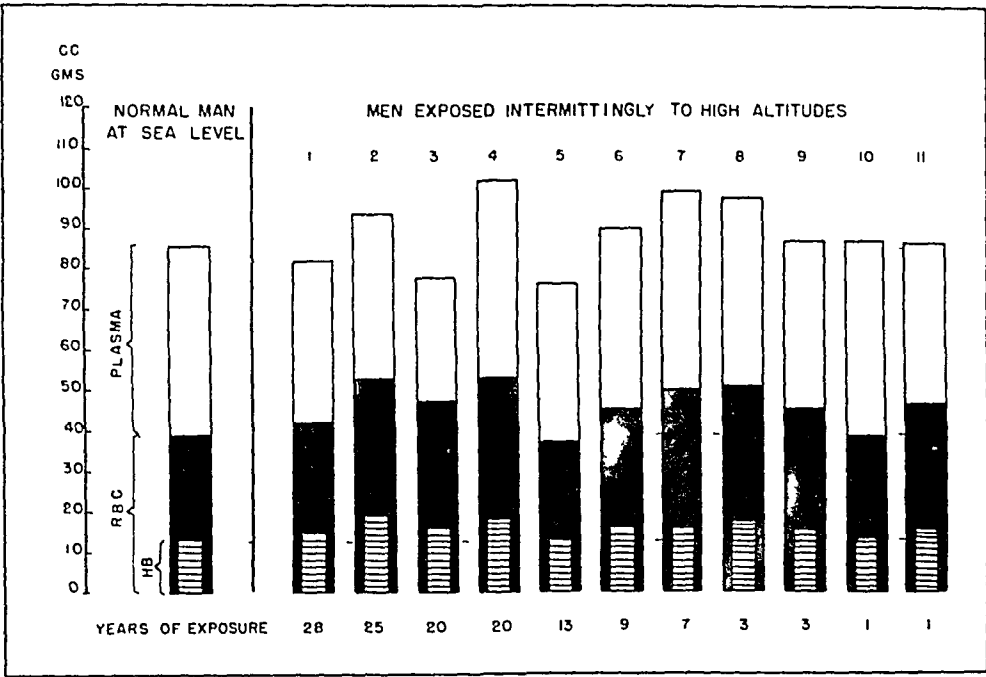


Chart 10—Blood volume (expressed in cubic centimeters and in grams per kilogram of body weight) of 11 men exposed daily to a low barometric pressure. The black zone represents red cell volume, the shaded zone, total hemoglobin, the white zone, plasma volume

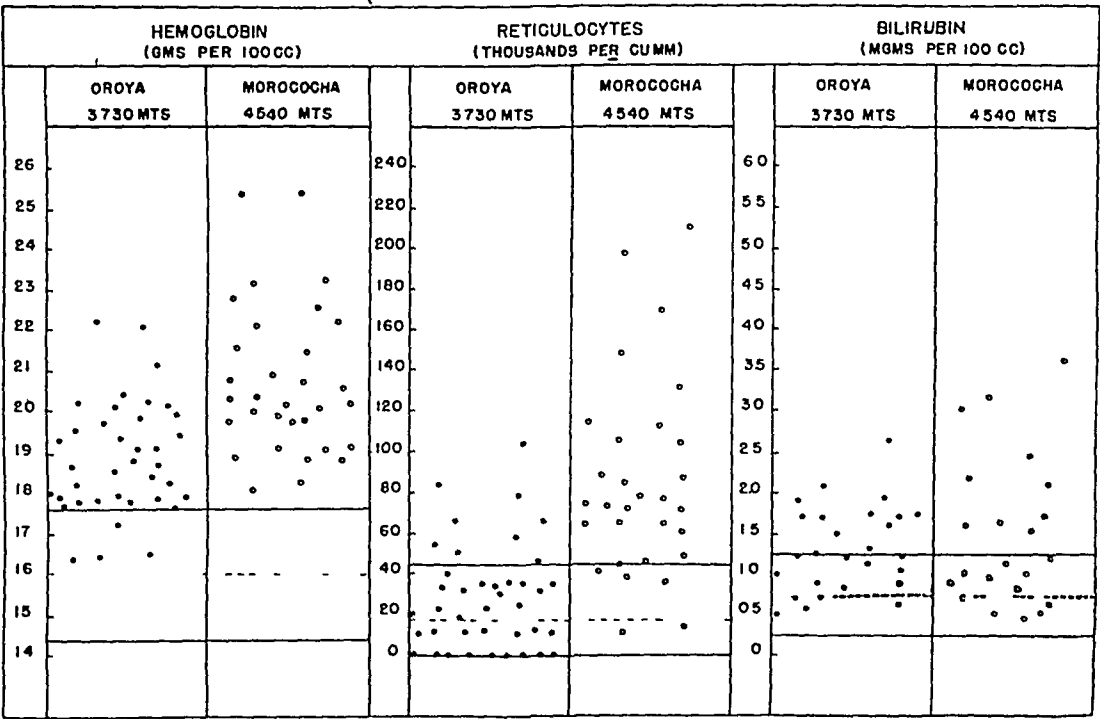


Chart 11—Values for hemoglobin, reticulocytes and bilirubin in healthy native residents of Oroya (at 3,730 meters, 12,240 feet) and Morococha (at 4,540 meters, 14,900 feet). The zones between the horizontal lines represent the limits of variation observed in healthy adult men at sea level

living permanently at high altitudes and subject, in consequence, to the constant influence of an anoxic condition (a) healthy Indian natives, (b) Indian natives who had contracted pneumoconiosis (silicosis) while working in the

Observations on Healthy Indian Natives—Observations were made on a total of 72 Indian natives, 40 of them living and studied in Oroya, at an altitude of 3,730 meters (12,240 feet), with an average barometric pressure of 482 mm of

TABLE 15—*Previous Observations on Blood of Residents of High Altitudes (Summary of Literature* ⁵³)

Investigators ⁵³	Place	Altitude, Meters	Number of Subjects	Red Blood Cells, Millions per Cu Mm	Hemoglobin, Gm per 100 Cc
Andresen, Mugrage	Denver	1,520	40	5.42	16.54
Fitzgerald	Colorado	1,550	5		15.84
Kuendy, Loewy and others ⁵⁴	Davos	1,580		6.55	
Liknaitzky	Johannesburg	1,750	60	5.99	(105.4%)
Stammers	Johannesburg	1,750	10		14.67
Fitzgerald	Colorado	1,830	6		15.02
Eggers	Mexico	2,250	22	7.25	(111.0%)
Fitzgerald	Colorado	2,370	10		16.40
Fitzgerald	Colorado	2,900	7		16.92
Fitzgerald	Colorado	3,080	9		17.16
Fitzgerald	Colorado	3,140	10		16.67
Hurtado, Guzman Barrón	Huancayo	3,260	10	5.82	
Fitzgerald	Colorado	3,450	22		17.46
Morales	La Paz	3,660	200	7.50	
Monge and others	Oroya	3,730	20	6.88	
Capdehourat and others	Catavi	3,750	11	6.31	
Fitzgerald	Colorado	4,300	16		18.05
Barcroft and others	O Pasco	4,330	15	7.05	
Barcroft and others	O Pasco	4,330	10		18.85
Hurtado	Morococha	4,540	100	6.66	15.93
Talbott and Dill	Quilchua	5,340	6	7.37	22.86

mercury, and 32 residents of Morococha, where they were investigated, at an elevation of 4,540 meters (14,900 feet), with a mean barometric pressure of 446 mm of mercury. The ages of these men varied between 19 and 48 years, but only 1 of them was in the fifth decade. Their

TABLE 16—*Degree of Anoxemia in Residents of Oroya and Morococha*

Place	Altitude		Average Barometric Pressure, No of		Arterial Oxygen Saturation, per Cent	
	Meters	Feet	Mm Hg	Sub jects	Mean \pm Extreme	
					P	E Variations
Oroya	3,730	12,240	482	15	87.6 \pm 0.27	84.4 - 90.2
Morococha	4,540	14,900	446	18	81.4 \pm 0.45	75.2 - 86.2

physical characteristics (average height, weight and surface area, 1.57 meters, 56.6 Kg and 1.57 square meters, respectively) corresponded to their race, and none gave a history of having worked in the mines for a prolonged time, a point of importance in these zones on account of the frequency of pneumoconiosis. All the observed men had been born either at the places,

TABLE 17—*Observations on Blood of Healthy Men Residents of Oroya (at an Altitude of 3,730 Meters, 12,240 Feet)*

Determinations	Number of Subjects	Mean \pm P E	St. Dev. \pm P E	Coefficient of Variation, %	Extreme Variations
Red blood cells (millions per cu mm)	40	5.67 \pm 0.04	0.39 \pm 0.03	6.9	4.70 - 6.28
Hematocrit (red cells, per cent)	40	54.1 \pm 0.41	3.9 \pm 0.21	7.2	47.8 - 65.4
Hemoglobin (Gm per 100 cc)	40	18.82 \pm 0.15	1.46 \pm 0.15	7.7	16.40 - 22.05
Corpuscular mean volume (cu microns)	40	95.2 \pm 0.58	5.5 \pm 0.41	5.8	84.2 - 113.1
Corpuscular mean diameter (microns)	40	7.88 \pm 0.03	0.24 \pm 0.02	3.0	7.42 - 8.62
Corpuscular mean thickness (microns)	40	1.97 \pm 0.02	0.17 \pm 0.01	8.6	1.48 - 2.22
Corpuscular mean surface area (sq microns)	40	145.8 \pm 0.47	5.1 \pm 0.33	3.5	133.6 - 158.0
Spherocytic index	40	0.25 \pm 0.002	0.03 \pm 0.001	12.0	0.17 - 0.30
Corpuscular mean hemoglobin (micromicrograms)	40	33.0 \pm 0.25	2.4 \pm 0.18	8.0	28.7 - 38.4
Corpuscular mean hemoglobin concentration (%)	40	34.8 \pm 0.10	0.9 \pm 0.06	3.0	32.1 - 36.6
Reticulocytes (per cent)	40	0.8 \pm 0.06	0.5 \pm 0.04	62.5	0 - 2.2
Reticulocytes (thousands per cu mm)	40	38.0 \pm 2.90	24.3 \pm 2.05	63.9	0 - 105.8
Red blood cell fragility	30				
Initial hemolysis (per cent)		0.46 \pm 0.001	0.01 \pm 0.001	2.2	0.44 - 0.50
Total hemolysis (per cent)		0.38 \pm 0.002	0.02 \pm 0.001	5.2	0.34 - 0.42
Blood viscosity	30	8.4 \pm 0.21	1.7 \pm 0.15	20.2	5.8 - 15.2
Bilirubin, total (mg per 100 cc)	30	1.47 \pm 0.09	0.71 \pm 0.06	48.3	0.56 - 4.38
Leukocytes (per cu mm)	40	6,500 \pm 155	1,258 \pm 109	19.2	3,400 - 9,600
Differential leukocytic count	40				
Neutrophils, stab (per cent)		5.0 \pm 0.30	2.8 \pm 0.21	56.0	0 - 2
Neutrophils, segmented (per cent)		52.8 \pm 1.13	10.6 \pm 0.79	20.1	32 - 79
Neutrophils, total (per cent)		57.9 \pm 1.13	10.6 \pm 0.79	18.3	37 - 86
Eosinophils (per cent)		2.5 \pm 0.22	2.1 \pm 0.15	84.0	0 - 10
Basophils (per cent)		0.1 \pm 0.007	0.7 \pm 0.005	700.0	0 - 3
Monocytes (per cent)		4.9 \pm 0.24	2.3 \pm 0.16	46.9	0 - 9
Lymphocytes (per cent)		34.8 \pm 1.02	9.6 \pm 0.72	27.6	11 - 54

TABLE 18—Observations on Blood of Healthy Men Residents of Morococha (at an Altitude of 4,540 Meters, 14,900 Feet)

Determinations	Number of Subjects	Mean ± P E	St Dev ± P E	Coeffi cient of Variation, %	Extreme Variations
Red blood cells (millions per cu mm)	32	6 15 ± 0 07	0 57 ± 0 05	9 3	4 97 - 7 59
Hematocrit (red cells, per cent)	32	59 9 ± 0 66	5 6 ± 0 47	9 3	52 2 - 76 2
Hemoglobin (Gm per 100 cc)	32	20 76 ± 0 20	1 71 ± 0 14	8 2	18 10 25 40
Corpuscular mean volume (cu microns)	32	97 5 ± 0 75	6 3 ± 0 53	6 5	85 5 106 8
Corpuscular mean diameter (microns)	32	7 74 ± 0 01	0 11 ± 0 01	1 4	7 31 8 01
Corpuscular mean thickness (microns)	32	2 08 ± 0 02	0 16 ± 0 01	7 7	1 70 - 2 41
Corpuscular mean surface area (sq microns)	32	145 0 ± 1 18	9 9 ± 0 83	6 8	133 6 - 153 6
Spherocytic index	32	0 27 ± 0 002	0 2 ± 0 001	7 4	0 21 - 0 32
Corpuscular mean hemoglobin (micromicrograms)	32	33 9 ± 0 29	2 5 ± 0 21	7 3	23 4 - 37 4
Corpuscular mean hemoglobin concentration (%)	32	34 7 ± 0 12	1 0 ± 0 08	2 9	33 2 37 4
Reticulocytes (per cent)	32	1 5 ± 0 07	0 6 ± 0 05	40 0	0 2 3 3
Reticulocytes (thousands per cu mm)	32	83 4 ± 5 35	44 9 ± 3 79	53 8	10 8 210 5
Bilirubin, total (mg per 100 cc)	20	1 56 ± 0 19	1 22 ± 0 13	78 2	0 45 4 91
Bilirubin, direct (mg per 100 cc)	20	0 46 ± 0 03	0 17 ± 0 02	36 9	0 16 - 0 86
Bilirubin, indirect (mg per 100 cc)	20	1 10 ± 0 17	1 10 ± 0 12	100 0	0 23 4 32
Leukocytes (per cu mm)	32	6,900 ± 144	1,212 ± 102	17 6	4,700 10,900
Differential leukocytic count	32				
Neutrophils, stab (per cent)		3 0 ± 0 22	1 3 ± 0 15	60 0	0 6
Neutrophils, segmented (per cent)		49 9 ± 1 34	10 9 ± 0 94	21 0	25 - 71
Neutrophils, total (per cent)		52 7 ± 1 33	10 8 ± 0 94	20 5	27 71
Eosinophils (per cent)		2 2 ± 0 15	1 2 ± 0 10	54 5	0 5
Basophils (per cent)		0 2 ± 0 02	0 5 ± 0 01	250 0	0 - 2
Monocytes (per cent)		5 5 ± 0 34	2 8 ± 0 24	50 9	1 - 13
Lymphocytes (per cent)		39 4 ± 1 29	10 5 ± 0 91	26 6	21 62

TABLE 19—Determinations of Blood Volume of Healthy Native Male Residents at High Altitudes

Determinations	A With Brilliant Vital Red (30 Subjects)			
	Mean ± P E	St Dev ± P E	Coeffi cient of Variation, %	Extreme Variations
1 In Oroya (at 3,730 Meters, 12,240 Feet)				
Blood volume (liters)	6 15 ± 0 12	1 03 ± 0 09	16 7	4 26 9,05
Blood volume (cc per Kg)	108 7 ± 1 69	13 7 ± 1 19	12 6	79 6 149 6
Plasma volume (liters)	2 76 ± 0 05	0 44 ± 0 03	15 9	1 94 - 3 72
Plasma volume (cc per Kg)	48 9 ± 0 87	7 1 ± 0 61	14 5	35 9 65 9
Red cell volume (liters)	3 36 ± 0 12	0 93 ± 0 08	29 1	2 22 5 67
Red cell volume (cc per Kg)	59 7 ± 1 07	8 7 ± 0 76	14 6	41 5 83 2
Total hemoglobin (Gm)	1,150 ± 28	226 ± 19	19 6	753 - 1,319
Total hemoglobin (Gm per Kg)	20 7 ± 0 40	3 3 ± 0 23	15 9	14 2 30 1
2 In Morococha (at 4,540 Meters, 14,900 Feet)				
	A With Brilliant Vital Red (6 Subjects)			
	Mean ± P E	St Dev ± P E	Coeffi cient of Variation, %	Extreme Variations
Blood volume (liters)	6 93 ± 0 50	1 50 ± 0 36	21 5	5 69 10 14
Blood volume (cc per Kg)	120 8 ± 4 03	13 5 ± 1 94	11 2	113 5 145 9
Plasma volume (liters)	2 65 ± 0 30	0 44 ± 0 10	16 6	2 00 3 59
Plasma volume (cc per Kg)	46 1 ± 1 27	4 2 ± 0 90	9 1	40 8 - 52 1
Red cell volume (liters)	4 29 ± 0 38	1 14 ± 0 27	26 6	3 03 - 6 59
Red cell volume (cc per Kg)	74 1 ± 3 86	12 8 ± 2 73	17 2	54 1 - 94 8
Total hemoglobin (Gm)	1,464 ± 123	364 ± 87	24 9	1,034 - 2,185
Total hemoglobin (Gm per Kg)	25 2 ± 1 17	3 9 ± 0 81	15 4	19 3 - 21 4
	B With Evans Blue (11 Subjects)			
	Mean ± P E	St Dev ± P E	Coeffi cient of Variation, %	Extreme Variations
Blood volume (liters)	5 89 ± 0 16	0 73 ± 0 11	13 2	5 01 7 53
Blood volume (cc per Kg)	100 3 ± 2 30	10 8 ± 1 62	10 8	86 4 - 125 4
Plasma volume (liters)	2 14 ± 0 06	0 27 ± 0 04	12 6	1 65 - 2 59
Plasma volume (cc per Kg)	36 2 ± 0 55	2 6 ± 0 39	7 2	32 3 40 8
Red cell volume (liters)	3 73 ± 0 15	0 71 ± 0 11	19 0	2 83 5 53
Red cell volume (cc per Kg)	64 1 ± 2 39	11 2 ± 1 69	17 5	49 7 - 92 7
Total hemoglobin (Gm)	1,293 ± 54 1	254 ± 33 2	19 6	997 - 1,925
Total hemoglobin (Gm per Kg)	22 0 ± 0 87	4 1 ± 0 61	18 6	17 2 - 32 1

or nearby, where they were investigated or at altitudes over 3,050 meters (10,000 feet), in the latter case with a long residence in Oroya or Morococha. For 15 residents of Oroya and 18 of Morococha arterial blood was obtained and analyzed for its oxygen saturation in order to determine the degree of anoxemia to which the hematologic characteristics corresponded. Tables 16, 17, 18 and 19 contain the results obtained in all the studies made for these series of subjects. In Oroya, the lower locality, where the mean arterial oxygen saturation was found to be 87.6 ± 0.27 per cent, with variations between 84.4 and 90.2 per cent, the mean hemoglobin content was 18.82 ± 0.15 Gm per hundred cubic

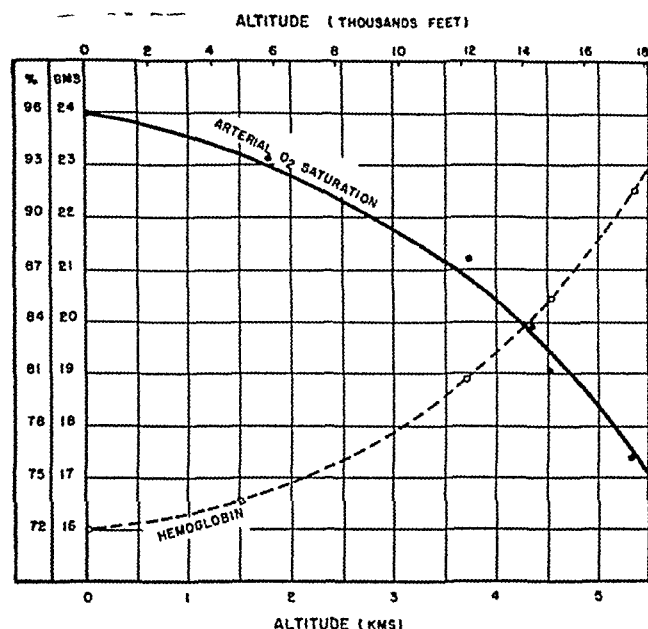


Chart 12—Relationship between the mean arterial oxygen saturation (per cent) and the mean hemoglobin content (grams per hundred cubic centimeters) in healthy male residents at different altitudes. The points used in the construction of the curves correspond to our observations and those made by Barcroft and others,³ Stammers,^{53f} Talbott and Dill^{53h} and Andresen and Mugrage⁵³ⁱ

centimeters, in 36 men (90 per cent) the concentration exceeded 17.50 Gm, with a maximal value of 22.05 Gm, and in only 4 subjects (10 per cent) it fell within the limits of variations seen at sea level (chart 11). The hematocrit reading also showed proportional increases, in 35 men (87.5 per cent) it was higher than 50.0 per cent red cells, with a maximal value of 65.4 per cent. In Morococha, the higher place, with a mean arterial oxygen saturation of 81.4 ± 0.45 per cent and variations between 75.2 and 86.2 per cent, the increases in the hemoglobin and hematocrit values were greater, as shown by the mean values of 20.76 ± 0.20 Gm and 59.9 ± 0.66 red cells per cent⁵⁴. All subjects had hemoglobin and hematocrit values over 17.50 Gm and 50.0 per cent, respectively, in 2 cases the high figures

of 25.40 Gm and 76.2 per cent were obtained.

The graphic correlation of the mean values of arterial oxygen saturation and the hemoglobin concentration corresponding to residents at sea level and at different altitudes obtained in previous investigations⁵⁵ and by us, in which the hemoglobin has been calculated from the accurate determination of the oxygen-binding capacity of

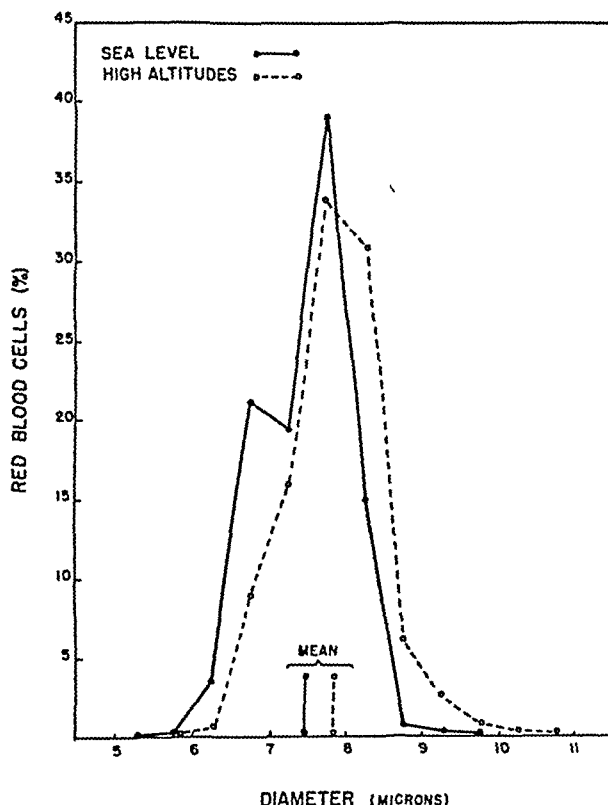


Chart 13—Diameter of the red blood cells at sea level and at high altitudes. The solid line represents measurements made for 130 healthy men living at sea level (a total of 39,400 cells measured), the interrupted line, measurements made for 72 healthy male residents of Oroya (at 3,740 meters, 12,240 feet) and Morococha (4,540 meters, 14,900 feet) (a total of 17,100 cells measured).

the blood, shows a striking inverse relationship between the degree of arterial oxygen saturation and the level of hemoglobin in the circulating blood (chart 12).

The morphologic characteristics of the red blood cells varied in some respects from those observed in healthy residents at sea level (table 20). The circulating erythrocyte at high alti-

⁵⁴ The mean value of 20.76 ± 0.20 Gm of hemoglobin is considerably higher than 15.93 ± 0.20 Gm, a mean obtained by one of us (A. H.)^{58a} in 1932 in observations made on healthy men living in the same locality. The reason for this discrepancy was found in a later investigation to be due to the water used for the dilution of the blood sample in the Sahli hemoglobinometer, a technic employed in the 1932 study, after addition of the water available in this place the color of the hematin solution faded rapidly, giving, in consequence, abnormal low values.

⁵⁵ Barcroft and others,³ Stammers,^{53f} Talbott and Dill,^{53h} Andresen and Mugrage.⁵³ⁱ

tudes has a larger size, as shown by an increased mean volume, diameter and surface area, the Price-Jones curves corresponding to the measurement of the diameter of several thousands of red cells at sea level and at high altitudes (chart 13) revealed a displacement to the right in the latter places, where 40.8 per cent of the cells had a diameter above 8.00 microns, as compared with 16.3 per cent at sea level, on the other hand, a diameter of less than 7.00 microns was observed in 24.9 per cent of the red cells of subjects studied at sea level, in contrast with 9.6 per cent at high altitudes. The tendency to a slight macrocytosis at high altitudes has been observed in previous investigations⁵³, mean corpuscular volumes of 96.2 and 94.1 cubic microns have been found for the native residents of Morococha and

TABLE 20—Morphologic Characteristics of the Red Blood Cells of Healthy Men (Residents) at Different Altitudes

	Lima	Oroya	Morococha
Altitude	Sea level	3,730 meters	4,540 meters
Number of subjects	175	40	32
	Mean ± P.E.		
Corpuscular mean volume (cu microns)	91.3 ± 0.23	95.2 ± 0.58	97.5 ± 0.75
Corpuscular mean diameter (microns)	7.48 ± 0.01	7.88 ± 0.03	7.74 ± 0.01
Corpuscular mean thickness (microns)	2.09 ± 0.01	1.97 ± 0.02	2.08 ± 0.02
Corpuscular mean surface area (sq microns)	137 ± 0.22	146 ± 0.47	145 ± 1.18
Spherocytic index	0.28 ± 0.01	0.25 ± 0.01	0.25 ± 0.01
Corpuscular mean hemoglobin (micromicrograms)	31.2 ± 0.09	33.0 ± 0.25	33.9 ± 0.29
Corpuscular mean hemoglobin concentration (%)	34.1 ± 0.07	34.8 ± 0.10	34.7 ± 0.12

Quilchua (at 4,540 and 5,340 meters, respectively) Talbott⁵⁶ reported an increase in the size of the red blood cells in the members of the Chilean High Altitudes Expedition after a prolonged residence. The high red cell count associated with the moderate increase in the cell volume at high altitudes makes the latter characteristic more significant, because at sea level a greater number of red cells per cubic millimeter is accompanied by a decreased cell size (table 4). The hemoglobin content of the red cells was found to be elevated in the residents of high altitudes as compared with the observations made at sea level, but the increase corresponded to their larger size, as shown by the corpuscular hemoglobin concentration (per cent), which was practically unchanged at all altitudes.

It has been postulated by some investigators⁵⁷ that the hemoglobin is distributed on the surface of the red cells, a statistical study of our observations on healthy men living at sea level and

at high altitudes (which include a total of 130 and 72 men, respectively) fails, however, to support such a view. The coefficients of correlation between mean corpuscular volume and mean corpuscular hemoglobin were found to be $+0.7791 \pm 0.0232$ and $+0.8636 \pm 0.0202$ for the series of subjects studied at sea level and at high altitudes, respectively, while the corresponding coefficients between mean corpuscular surface area and mean corpuscular hemoglobin were $+0.5272 \pm 0.0427$ and $+0.4503 \pm 0.0633$.

The mean values for the reticulocytes, in per cent and per cubic millimeter, were higher than the corresponding ones at sea level, and the increase was especially marked at the higher altitude (Morococha), where the large majority of the natives showed values well above the upper sea level limit of variation (chart 11), the highest observed value was 3.3 per cent. Barcroft and his collaborators³ found that 5 native residents of Cerro de Pasco (4,330 meters, 14,200 feet of altitude) had reticulated counts between 1.2 and 2.0 per cent, with an average of 1.5 per cent, and that 4 American residents had counts between 1.3 and 1.5 per cent. At the extremely high elevation of 5,340 meters (17,500 feet) Talbott and Dill⁵⁸ observed counts of 0.4, 0.6 and 3.4 per cent in the blood of 3 residents. No nucleated red cells in the peripheral blood have been observed in previous investigations or by us in residents of high altitudes.

A definite rise was observed in the serum bilirubin, which confirmed previous but less complete observations^{53c, e}. The mean values of 1.47 ± 0.09 and 1.56 ± 0.19 mg per hundred cubic centimeters, obtained in Oroya and in Morococha, respectively, indicated approximately 100 per cent increase over the mean normal value at sea level, and in the majority of the subjects the pigment was present in a concentration exceeding 1.00 mg per hundred cubic centimeters (chart 11). At the higher altitude (4,540 meters, 14,900 feet) we determined the bilirubin in its total and fractionated forms in 20 natives, it was found that the increase affected almost exclusively the indirectly determined pigment, the ratio direct total bilirubin had an average value of 29.5 per cent, in contrast with 51.4 per cent observed at sea level.

The bilirubin-excretory function of the liver was investigated in 4 native residents of Moro-

57 Burker, K. Arch f Physiol 195 516, 1922. Brinkman, R., and Szent-Gyorgy, A. J Physiol 58. 204, 1923. Rabinowitch, I. M., and Stearn, G. Hemoglobin Content of Red Blood Cells in Relation to Their Surface Area, Arch Int Med 34 124 (July) 1924.

56 Talbott, J. H. Folia haemat 55 23, 1936.

cocha by injecting 50 mg of bilirubin and determining its concentration in the blood three hours after the injection (method of von Bergman, quoted by Dameshek and Singer²³), the same men were brought down to sea level ten days later, where the test was repeated twenty to thirty-six hours after arrival. For comparative purposes the same test was performed for 4 residents of sea level and repeated immediately after their arrival to Morocochoa. The results obtained in the sixteen tests are given in chart 14. The 4 natives studied in Morocochoa, all with an

way in 3 of them, in 1 it was practically unchanged. No significant alterations were observed in the group of 4 men studied first at sea level and later on arrival at high altitude in regard to the basal pigment and the degree of retention of the injected bilirubin. The viscosity of the blood of 30 native residents of Oroya (3,730 meters, 12,240 feet) had a mean value of 84 ± 0.21 with a standard deviation of 17, figures which are distinctly higher than the corresponding ones, of 4.64 ± 0.025 and 0.86 , obtained by Nygaard, Wilder

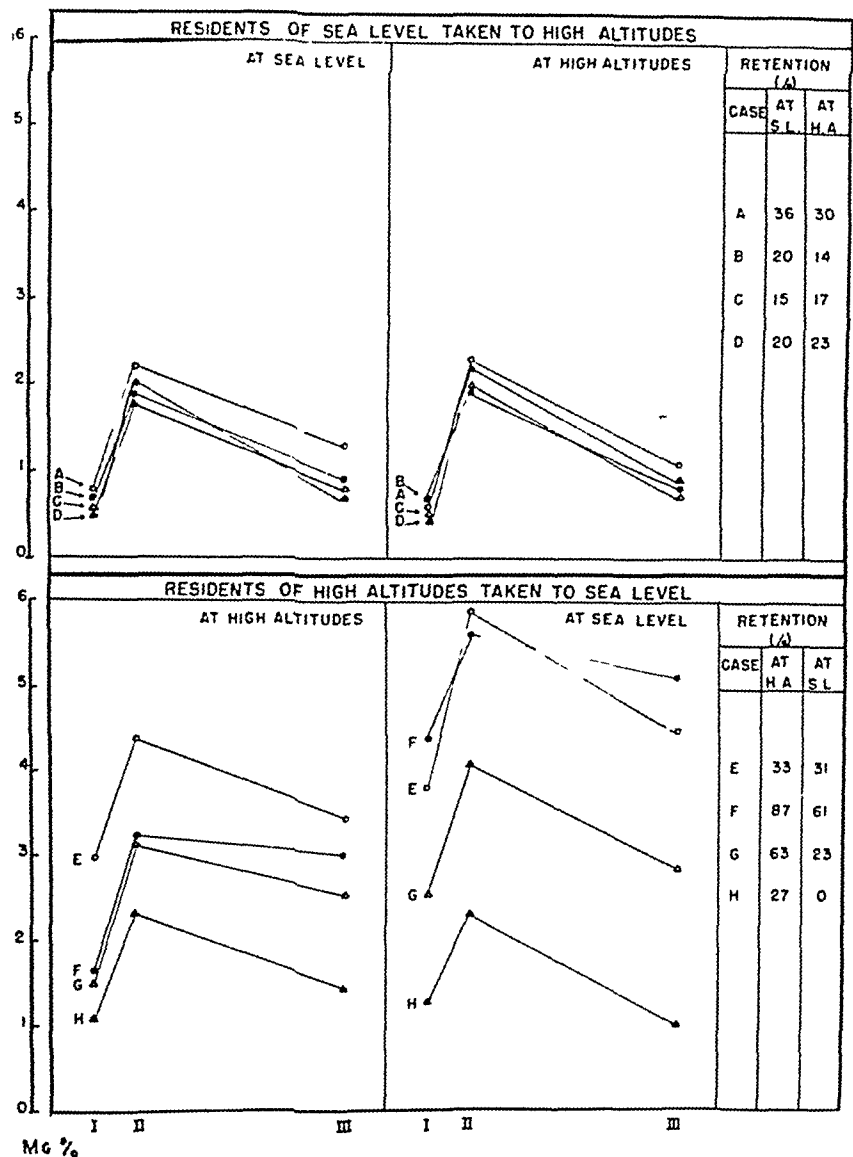


Chart 14—Results of bilirubin excretion tests of healthy men at sea level and at high altitudes. *I*, basal serum bilirubin, *II*, serum bilirubin five minutes after an intravenous injection of 50 mg, *III*, serum bilirubin three hours after the injection. Notice the increase in the basal bilirubin which occurs when men living at high altitudes are brought down to sea level.

initial bilirubin concentration above 1.00 mg per hundred cubic centimeters, showed a higher degree of retention of the injected bilirubin than the men studied at sea level, in 2 of them the retention was marked (62.9 and 86.7 per cent), when brought down to sea level all showed an increase in the basal value for bilirubin, but, on the other hand, the excretion of the injected pigment was accomplished in a more complete

and Berkson⁵⁸ for 503 subjects studied at sea level. Holbrook and Watson⁵⁹ found, also at sea level, an average value of 5.08, with variations between 4.0 and 6.0, in 97 normal subjects.

58 Nygaard, K. K., Wilder, M., and Berkson, J. *Am J Physiol* **114**: 128, 1935.
59 Holbrook, A. A., and Watson, B. M. *Am J M Sc* **198**: 750, 1939.

The fragility of the red blood cells to hypotonic solutions of sodium chloride was found to be essentially normal in the subjects investigated in Oroya. The mean values, of 0.46 ± 0.001 and 0.38 ± 0.002 per cent, for initial and total hemolysis, respectively, were the same as those obtained at sea level. Only in 2 subjects the values obtained for initial hemolysis were slightly higher than the upper limit observed at sea level, which showed some evidence of increased fragility.

The number of leukocytes per cubic millimeter did not show any significant alteration in the native residents of high altitudes. The mean observed values in Oroya and Morococha were almost identical with the one observed at sea level, in only 1 subject at the higher altitude, a slight leukocytosis (10,900 white cells per cubic millimeter) was observed. On the other hand, the differential leukocyte count when compared with the sea level values showed a mean percentage increase in the lymphocytes, more marked the higher the altitude, with a corresponding decrease in the segmented neutrophils and eosinophils and, to a lesser degree, in the monocytes, the mean values of the stab neutrophils and basophils did not show any appreciable change. This relative lymphocytosis has been observed in previous investigations made at high altitudes, these have been summarized by Loewy and Wittkower^{53j}. In this respect it is interesting to mention that the variation in the differential leukocyte count has been found to exist in residents of elevations below 2,000 meters (6,560 feet)⁶⁰.

The circulating blood volume was investigated for 47 healthy Indian natives, 30 of them residents of Oroya (at 3,730 meters, 12,240 feet) and 17 residents of Morococha (at 4,540 meters, 14,900 feet). In the latter place 11 of the determinations were carried out by means of injection of the dye Evans' blue (method of Gibson and Evans⁶¹), all the others were made with the dye brilliant vital red⁶². The results obtained in both places agreed in the finding of an increased total cell volume in all subjects investigated, but the degree of the increase was not similar in the two methods (table 19). In Oroya, the lower place, the cell volume, expressed in cubic centimeters per kilogram of body weight, showed a mean increase of 59.7 per cent over the corresponding sea level value, in Morococha, the higher altitude, the mean increase was 90.9 per cent with the brilliant vital

red method and 65.2 per cent with the Evans' blue. The plasma volume, in cubic centimeters per kilogram of body weight, was found to be practically unchanged at both altitudes, according to the determinations made with brilliant vital red, but had an average decrease of 23.1 per cent in Morococha, in those men in whom the Evans' blue dye was employed.

The discrepancy between the results obtained by the two dye methods cannot be strictly attributed to their different technical characteristics, the small number of subjects studied in each series may be an important factor in explaining the higher cell volume observed with the brilliant vital red. In a recent observation, not included in this paper, a determination of the blood volume made for 1 healthy native resident of Morococha by means of the dye Evans' blue gave the values of 165.2, 32.0 and 132.3 cc of blood, plasma and red cells, respectively, per kilogram of body weight. Another indication of the possible accuracy of the results observed with brilliant vital red is the high correlation coefficient, of $+0.8008 \pm 0.0269$, obtained between the hematocrit level and the total red cell volume of 79 subjects studied at high altitudes with this dye method (including healthy natives and persons with pathologic conditions, the latter to be discussed in the next chapter). An analogous correlation has been found to exist in cases of polycythemia vera,⁶¹ in the study of which Evans' blue dye was employed, and in dogs investigated by means of radioactive iron⁶².

Taking into consideration the objections which have been raised in regard to the use of the hematocrit in the determination of the total blood volume and the recent criticisms⁶³ concerning the accuracy of the linear extrapolation for the calculation of the plasma volume with Evans' blue dye, it seems appropriate at the present time to stress the value of comparative studies made with similar techniques rather than the strict significance of absolute figures obtained by a given method. In reviewing the importance of determinations of blood volume Keith⁶⁴ has recently remarked that "the ideal method of estimating plasma and blood volume has still to be discovered."

The existence of a polycythemic normovolemia or hypervolemia in residents of high altitudes has been demonstrated in previous investigations made at moderate elevations. Lippmann,⁶⁵ in 1926, obtained average values of 87.3, 40.2 and 47.1 cc of blood, plasma and red cells per kilogram of body weight in 4 men living in Davos, at an altitude of 1,590 meters (5,000 feet), Lozoya Solis⁶⁶ in 1936, determined the blood volume of 53 healthy men living in the city of Mexico, located at an altitude of 2,260 meters (7,410 feet) and found mean values of 92.4 and

61 Gibson, J. G. *Ann Int Med* **14**: 2014, 1941.

62 Hahn, P. H., and Bale, W. T. *Am J Physiol* **136**: 314, 1942.

63 King, B. G., Cole, K. S., and Oppenheimer, E. T. *Am J Physiol* **138**: 636, 1943. Davis⁶⁰ⁱ

64 Keith, N. M. *J Mt Sinai Hosp* **8**: 692, 1942.

65 Lippmann, A. *Klin Wchnschr* **5**: 1406, 1926.

66 Lozoya Solis, I. *Arch latino-am de cardiol y hemat* **6**: 241, 1936.

60 Ruppner, E. *Schweiz med Wchnschr* **50**: 105, 1920. Stammers, A. D. *J Physiol* **78**: 335, 1933. Peterson, R. F., and Peterson, W. G. *J Lab & Clin Med* **20**: 723, 1935. Fitzgerald^{57a}

507 cc of blood and red cells per kilogram of body weight, which he considered to represent increases of 87 and 127 per cent, respectively, over the sea level values. The plasma volume was unchanged. The correlation of our findings with those obtained in these investigations seems to indicate that there is an inverse relationship between the volume of circulating red cells, expressed in cubic centimeters per kilogram of body weight, and the arterial oxygen saturation. The higher the altitude and the degree of anoxemia, the more marked is the increase in the cell volume, while the plasma volume remains unchanged or decreases.

The polycythemia associated with constant exposure to a low barometric pressure has also been long since verified in animals living at high altitudes.⁶⁷ Izquierdo^{67a} cited the investigations of Vergara Lopez, who in studies made in the city of Mexico in 1899 found an increase of red blood cells in guinea pigs. Hall Dill and Barron^{67c} observed an increased amount of hemoglobin in the blood of sheep and rabbits living at altitudes over 3050 meters (10,000 feet), these investigators made the interesting observation that in the llama, a native animal of the high Andean plateau, an increasing level of altitude corresponded to a decreasing amount of hemoglobin in the blood. Rotta^{67d} has observed in dogs living in Morococha (at 4,540 meters, 14,900 feet) changes in the blood volume parallel to those found by us in the Indian native residents of that place, in determinations made in 9 dogs he found an increase of 44.5 per cent in the red cell volume while the plasma volume was almost identical to the one observed in the comparative studies made at sea level (table 21).

TABLE 21—*Determinations of Blood Volume* of Dogs at Sea Level and in Morococha (at 4,540 Meters, 14,900 Feet) Data Taken from Rotta^{67d}*

	Sea Level	Morococha
Number of dogs	8	9
Average weight (Kg)	9.0	7.6
	Mean \pm P. F.	
Blood volume (cc per Kg)	80.7 \pm 1.04	96.0 \pm 2.62
Plasma volume (cc per Kg)	45.9 \pm 0.94	45.7 \pm 1.50
Red cell volume (cc per Kg)	34.6 \pm 1.14	50.0 \pm 2.22
Hemoglobin (Gm per Kg)	11.0 \pm 0.27	15.4 \pm 0.31

* With dye brilliant vital red.

67 (a) Izquierdo, J. J. *Compt rend Soc de biol* 87:1195, 1922. (b) Mulligan, R. M. *Am J Physiol* 133:394, 1941. (c) Hall, F. G., Dill, D. B., and Barron, E. S. G. *J Cell & Comp Physiol* 8:301, 1936. (d) Rotta, A. *La circulacion en las grandes alturas*, Lima, Facultad de Medicina, 1938.

Observations in Cases of Pneumonocomosis (Silicosis)—Studies were made in Oroya (at an altitude of 3,730 meters [12,240 feet]) on 82 persons who had silicosis acquired while they were working in mines located at high altitudes. Owing to the anatomic alterations in the lungs these patients often showed an abnormal accentuation of the arterial oxygen unsaturation present in some degree in all dwellers of high altitudes. It was, in consequence, interesting to investigate the effects of this increased degree of anoxemia on the hematologic characteristics of the circulating blood.

All the silicotic persons were Indian natives born and living at high altitudes, their ages varied between 25 and 56 years. Their physical characteristics corresponded to their race, and, with few exceptions, undernourishment was not revealed by the clinical examination. The diagnosis of silicosis was made with consideration of the occupational history (exposure to siliceous dust while working in the mines) and the findings in the roentgenogram of the chest. The pulmonary lesions fluctuated from discrete nodulations to large areas of confluent fibrosis. No person with tubercle bacilli in the sputum or with an obvious associated tuberculosis has been included in this series. In each case in addition to and simultaneous with the taking of the venous blood sample on which the different hematologic studies were carried out, an arterial puncture was made and the blood taken analyzed for its carbon dioxide content and oxygen saturation. The latter varied between 43.3 and 90.8 per cent. Forty of the men showed a saturation of 84.0 per cent or higher, corresponding to that found in the healthy residents of the altitude where the investigations were made, in 33 it varied between 72.0 and 83.9 per cent, in 5 it was found to fluctuate between 60.0 and 71.9 per cent, and, finally, in the remaining group of 4 the arterial oxygen saturation was less than 60.0 per cent, the lowest value being 43.3 per cent. The last two groups included 4 silicotic men with obvious clinical signs of an associated circulatory insufficiency. The results obtained in the different investigations on the blood are given in relation to the degree of anoxemia, in tables 22 and 23 and presented graphically in charts 15 and 16.

Men with silicosis in whom no accentuation of the degree of anoxemia was caused by the pulmonary lesions presented hematologic characteristics similar to those observed in the healthy

residents of the altitudes where they lived⁶⁸ On the other hand, silicotic men with an abnormal and more pronounced unsaturation of the arterial blood showed definite rises in the concentration of red blood cells and hemoglobin, which were, up to a certain limit, greater the

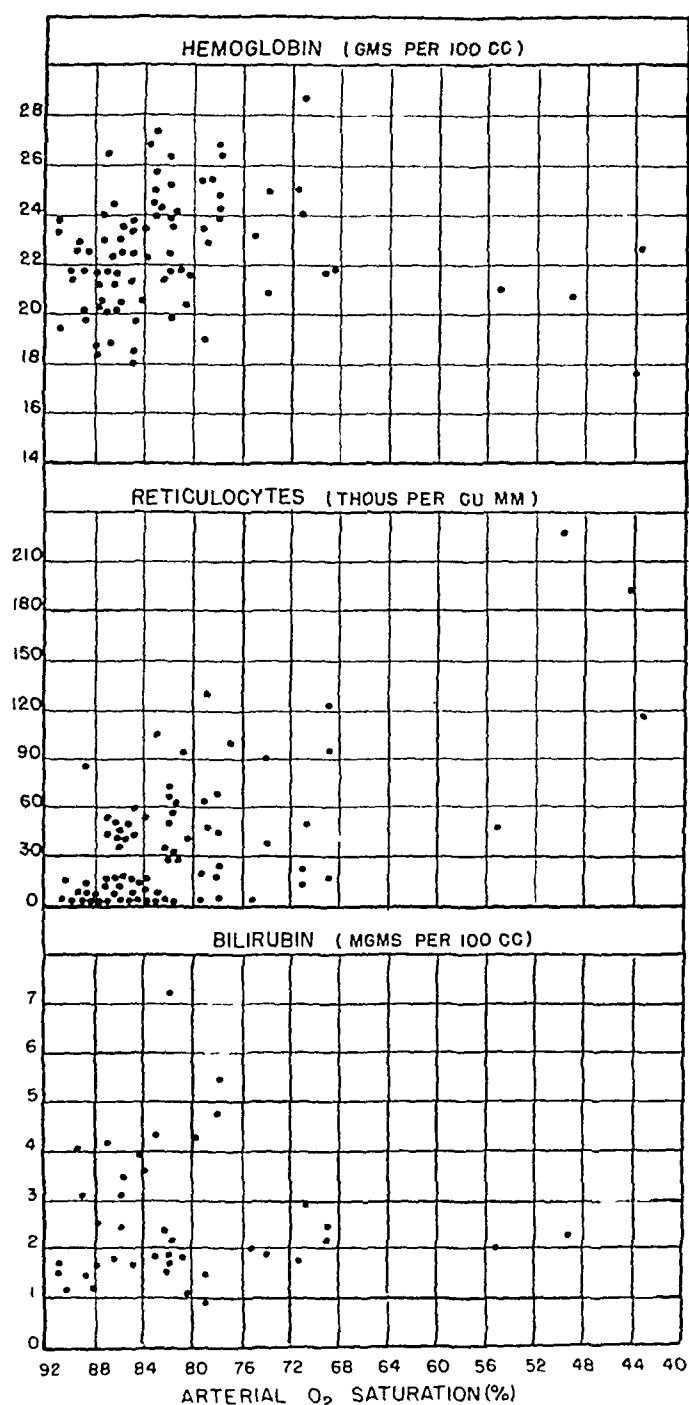


Chart 15—Relation between values for hemoglobin, reticulocytes and bilirubin and the degree of arterial oxygen saturation in persons with silicosis studied at high altitudes

higher the degree of anoxemia. The 3 highest hemoglobin and hematocrit values observed were

68 All the men with silicosis lived at altitudes of about 4,200 to 4,500 meters (13,800 to 14,800 feet), where the mines were located, but the study was made one or two days after their arrival at Oroya, at an altitude of 3,730 meters (12,240 feet). Thus, the arterial oxygen saturation found in the investigations corresponded to the latter altitude, while the hematologic characteristics were related to the influence of the higher altitudes where they lived

26.89, 27.47, 28.68 Gm per hundred cubic centimeters and 81.1, 81.2 and 82.3 per cent red cells, respectively. The determination of the blood volume of the respective subjects revealed, similarly, a marked increase in the cell volume, also in proportion to the degree of anoxemia, accompanied by a decreased plasma volume. In 11, or 25 per cent of the cases studied, the blood volume was higher than 150 cc per kilogram of body weight, and in 13 cases, or 29.5 per cent, the red cell volume, similarly expressed, was higher than 100 cc. In a case of advanced silicosis, studied subsequently and not included in this series, a determination of blood volume made with Evans blue dye gave the following results: 150.2, 48.2 and 101.2 cc of blood, plasma and red cells, respectively, per kilogram of body weight.

These men with silicosis, all studied at the same altitude and showing great variability in the degree of anoxemia and in the level of polycythemia, offered a good opportunity to investigate the possible influence of other factors, in addition to the arterial oxygen insaturation, on the hematologic characteristics. In regard to the carbon dioxide content of the arterial blood, an increase of which has been cited as capable of eliciting a polycythemic response,⁶⁹ a correlation coefficient of -0.3275 ± 0.0686 was obtained between the arterial content of this gas (in volume per cent) and of hemoglobin (grams per hundred cubic centimeters), in contrast to the one of -0.4265 ± 0.0629 obtained between the arterial oxygen saturation (in per cent) and the hemoglobin (similarly expressed). Both correlations were linear (no significant difference with the correlation ratios) and independent of each other (the partial correlation coefficients had the same values).

The possibility of an unequal distribution of red blood cells in the vascular system, a factor which in the past has been thought to explain, at least in part, the polycythemia of high altitudes,⁷⁰ also has been investigated for 44 subjects (some of whom were healthy men). Red blood cell counts were made on samples of capillary and venous blood taken simultaneously; the mean observed counts were 6.30 ± 0.09 and 6.21 ± 0.10 millions per cubic millimeter, respectively, in 66 per cent of the cases the capillary count was higher than the venous, the average difference being 0.24 millions. In 15 cases of silicosis the red cell count was determined on samples of capillary, venous and arterial blood taken simultaneously; the mean values (millions of red cells per cubic millimeter) corresponding to these series of determinations were found to be as follows: capillary blood, 7.52 ± 0.22 , venous blood, 7.33 ± 0.20 , arterial blood, 7.19 ± 0.21 . The differences between these mean values have no statistical significance. Finally, in 19 cases of silicosis a hematocrit determination was made on venous and on arterial blood, also taken simultaneously; the mean observed values were 69.6 ± 1.15 and 69.7 ± 1.14 per cent red cells, respectively. These results show that the degree of polycythemia was essentially similar

⁶⁹ Jordan, H. E. and Speidel, C. C. *J. Exper. Med.* 40: 1, 1924.

⁷⁰ Campbell, W. A., and Hoagland, H. W. *Am. J. M. Sc.* 122: 654, 1901. Foà, C. *Lab. sc. internat. du Mont Rosa, Turin* 1: 15, 1904. Goyda, T. *Chem. Zentralbl.* 1: 672, 1911.

in the different sections of the vascular system, with a slight tendency to be higher in the capillary circuit

The various morphologic characteristics of the circulating erythrocytes were similar to those found in the group of healthy natives, a slight macrocytosis and a normal corpuscular hemoglobin concentration were the essential findings. Fewer reticulocytes were observed in these subjects, this was perhaps related to the fact that they were studied at an altitude lower than their habitual place of residence. The serum bilirubin was elevated in almost all the subjects, in 12 men, or 27.3 per cent of the total, the concen-

A certain degree of equilibrium between formation and destruction of blood seems to be attained in these persons with severe anoxia and marked polycythemia, administration of phenylhydrazine to a silicotic patient who had a red cell count of 10,630,000 per cubic millimeter (the highest count observed by us at high altitudes) caused a sharp increase in the serum bilirubin followed by a definite accentuation of the reticulocytosis (chart 17). Study of the data presented in tables 22 and 23 and in charts 15 and 16 indicates that the stimulating effect of the anoxic stimulus in eliciting a polycythemic

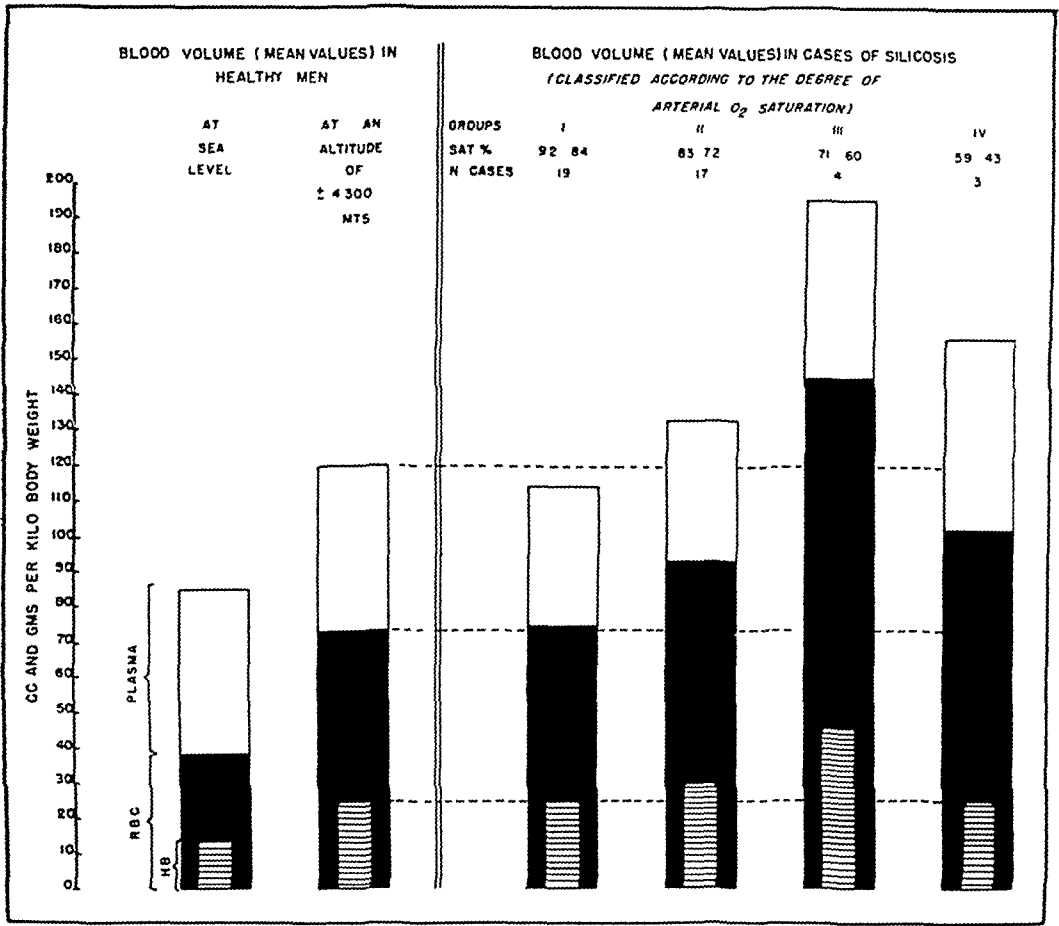


Chart 16—Mean blood volumes for four groups of men with silicosis studied* at high altitudes, arranged according to the degree of arterial oxygen saturation (The black zone represents red cell volume, the shaded zone, total hemoglobin, the white zone, plasma volume)

tration exceeded 300 mg per hundred cubic centimeters, and the highest observed values were 4.67, 5.55 and 7.24 mg. The viscosity of the blood was greatly augmented, and the mean values obtained for the different groups of subjects revealed about 100 per cent increase over the corresponding values for the healthy residents, the highest observed viscosity was 32.0. The coefficient of correlation between the hematocrit level and the viscosity of the blood, calculated from all the observations made on healthy and on pathologic subjects, was $+0.8205 \pm 0.0227$, a coefficient similar to the one obtained by Nygaard, Wilder and Berkson⁵⁸ in investigations made at sea level.

response had a well defined limit in the cases we are discussing. The greatest increases in the hemoglobin and hematocrit values were observed in men who had an arterial oxygen saturation between 70.0 and 86.0 per cent. The polycythemic hypervolemia attained its highest values in the same group of cases. With saturations of approximately 68.0 per cent or less there was a decrease in the hemoglobin and red cell volume, accompanied by a higher plasma volume (chart 18) and a greater number of reticulocytes (but in no case, regardless of the degree of anoxemia, were nucleated red cells found in the peripheral blood), the plasma bilirubin did not increase. The correlation of the arterial oxygen saturation

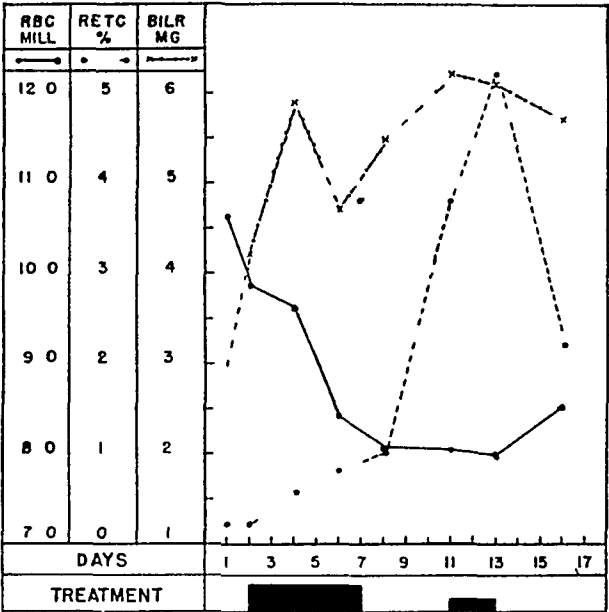


Chart 17—Values for red blood cells, reticulocytes and bilirubin determined during the administration of phenylhydrazine to a silicotic patient with a high level of polycythemia. Observations made at high altitudes

the mean arterial oxygen saturation was 76.2 per cent, on further ascent to an altitude of 6,140 meters (20,140 feet), which reduced the mean saturation to 65.6 per cent, a decrease in the hemoglobin and red blood cells was observed, Talbott suggested an increased rate of destruction of blood as the possible etiologic factor for this decrease

The high level of polycythemia found in men with silicosis was not associated with a corresponding increase in the number of leukocytes per cubic millimeter (table 22). Even the subjects who had a pronounced degree of anoxemia or a high level of polycythemia failed to show significant variations in the concentration of white blood cells, the differential leukocyte count, determined for 20 of these men, revealed frequent increases in the percentage value of stab neutrophils, but in no instance were metamyelocytes observed (table 24). The lack of correlation between the number of red and of white

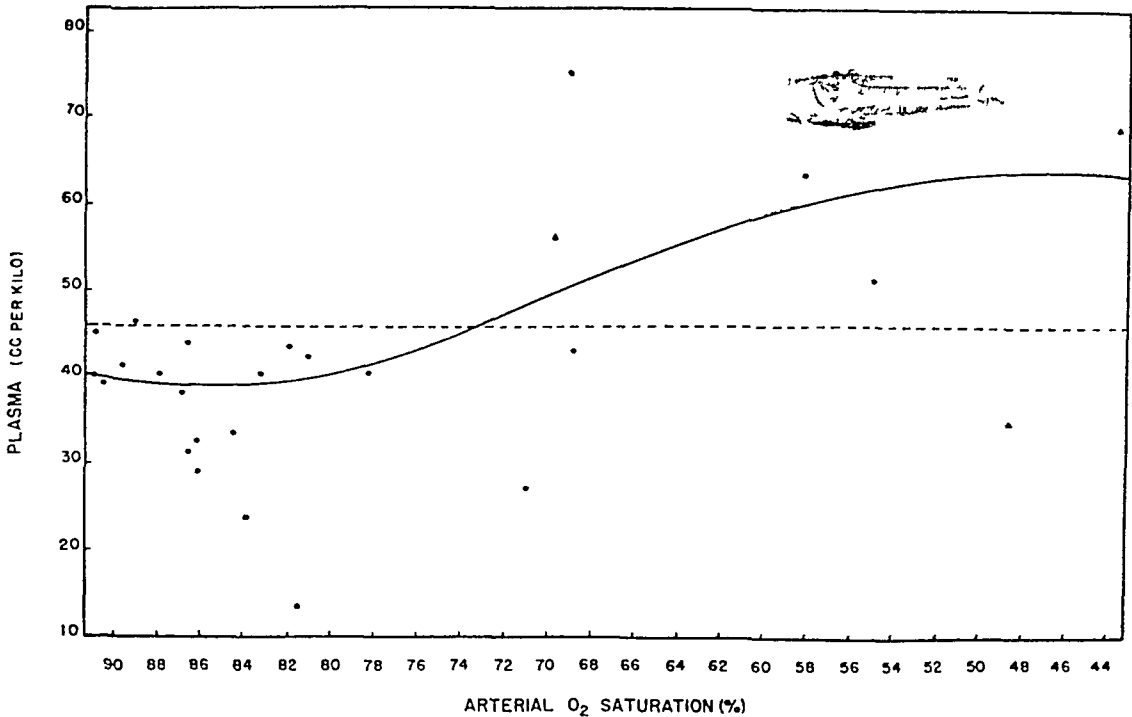


Chart 18—Plasma volume in relation to the degree of arterial oxygen saturation in 43 patients with silicosis studied at high altitudes. The horizontal interrupted line represents the mean plasma volume for healthy native residents (determinations made with brilliant vital red dye)

with the concentration of hemoglobin in the circulating erythrocytes revealed that an increasing degree of anoxemia was associated with a gradual diminution in the amount of hemoglobin held by the red cells (chart 19), in this connection it was also significant to find a decreased mean corpuscular volume in the men who had an unusually high arterial insaturation (table 22). The observations made by Talbott⁵⁶ on the members of the High Altitude Expedition to the Chilean Andes have a related significance, the highest level of polycythemia was found at an elevation of 5,340 meters (17,500 feet) where

blood cells in the peripheral blood and the absence of leukocytosis as a response to a condition of chronic anoxemia may be appreciated in chart 20

Chemical study of the gastric contents in hematologic disorders has attained a considerable interest in recent years. Most of this relates to the causative mechanism of various anemic processes, but it has been suggested⁷¹ that variations in the gastric acid content induce

⁷¹ Lombardi, E, and Cino, J. A. *Riforma med* 52 1343, 1936

TABLE 22—Observations on Blood of Patients with Silicosis Grouped According to the Degree of Anoxemia (Study Made at an Altitude of 3,730 Meters, 12,240 Feet)

	Arterial O ₂ Saturation			
	84% or More 40	72 0 83 9 % 33	60 0 71 9 % 5*	Less Than 60 0 % 4†
Number of cases				
Red blood cells (millions per cu mm)				
Mean ± P E	6 65 ± 0 10	7 72 ± 0 09	7 99 ± 0 49	7 98 ± 0 53
Standard deviation ± P E	0 90 ± 0 07	0 80 ± 0 06	1 47 ± 0 35	1 35 ± 0 37
Coefficient of variation (%)	15 5	10 3	18 4	16 9
Extreme variations	4 58 8 36	5 64 9 22	6 46 10 63	5 83 9 66
Hematocrit reading (red cells, per cent)				
Mean ± P E	63 7 ± 0 65	71 6 ± 0 82	74 7 ± 2 12	67 9 ± 2 34
Standard deviation ± P E	6 1 ± 0 16	7 0 ± 0 58	6 3 ± 1 50	6 0 ± 1 65
Coefficient of variation (%)	9 5	9 8	8 4	8 8
Extreme variations	51 8 80 1	58 7 81 2	66 2 - 82 3	58 5 - 74 1
Hemoglobin (Gm per 100 cc)				
Mean ± P E	21 52 ± 0 10	23 77 ± 0 24	24 26 ± 0 85	20 58 ± 0 72
Standard deviation ± P E	1 87 ± 0 14	2 04 ± 0 17	2 53 ± 0 60	1 86 ± 0 51
Coefficient of variation (%)	8 6	8 5	10 4	9 0
Extreme variations	18 03 26 64	19 20 27 47	21 77 28 68	17 66 - 22 72
Corpuscular mean volume (cu microns)				
Mean ± P E	96 7 ± 1 19	92 8 ± 1 00	95 4 ± 4 15	88 2 ± 8 03
Standard deviation ± P E	11 2 ± 0 84	8 2 ± 0 68	12 3 ± 2 93	20 6 ± 5 60
Coefficient of variation (%)	11 5	8 8	12 9	23 3
Extreme variations	80 0 120 9	77 1 106 2	76 4 109 9	72 4 123 7
Corpuscular mean hemoglobin (micromicrograms)				
Mean ± P E	32 7 ± 0 33	31 1 ± 0 31	31 1 ± 1 69	26 9 ± 2 72
Standard deviation ± P E	3 1 ± 0 23	2 9 ± 0 24	5 0 ± 1 19	7 0 ± 1 92
Coefficient of variation (%)	9 4	9 3	16 0	26 0
Extreme variations	27 5 41 3	26 1 38 6	23 5 35 7	21 6 - 35 9
Corpuscular mean hemoglobin concentration (%)				
Mean ± P E	33 9 ± 0 09	33 3 ± 0 13	32 4 ± 0 50	30 3 ± 0 54
Standard deviation ± P E	0 9 ± 0 07	1 1 ± 0 09	1 5 ± 0 36	1 4 ± 0 38
Coefficient of variation (%)	2 6	3 0	4 6	4 6
Extreme variations	31 4 35 4	31 2 36 7	30 0 34 9	28 2 - 31 5
Reticulocytes (per cent)				
Mean ± P E	0 6 ± 0 07	0 7 ± 0 06	0 6 ± 0 20	1 9 ± 0 27
Standard deviation ± P E	0 5 ± 0 05	0 5 ± 0 04	0 6 ± 0 14	0 7 ± 0 19
Coefficient of variation (%)	83 3	71 4	100 0	36 8
Extreme variations	0 1 4	0 2 2	0 2 2 0	0 6 2 4
Leukocytes (per cu mm)				
Mean ± P E	6,600 ± 220	6,770 ± 173	6,350 ± 779	7,330 ± 604
Standard deviation ± P E	2,000 ± 155	1,480 ± 122	2,310 ± 552	1,550 ± 426
Coefficient of variation (%)	31 2	21 7	36 3	21 1
Extreme variations	4,640 18,280	4,360 11,200	2,680 10 600	5,360 8 960

* Includes 1 patient with circulatory insufficiency

† Includes 2 patients with circulatory insufficiency

TABLE 23—Observations on Blood of Patients with Silicosis Grouped According to the Degree of Anoxemia (Study Made at an Altitude of 3,730 Meters, 12,240 Feet)

	Arterial O ₂ Saturation			
	84% or More 19	72 0 83 9 % 17	60 0 71 9 % 4*	Less Than 60 0 % 3†
Number of cases				
Blood volume (cc per Kg)				
Mean ± P E	114 6 ± 2 72	133 5 ± 4 27	191 3 ± 21 6	156 6 ± 5 06
Standard deviation ± P E	17 6 ± 1 92	26 1 ± 3 01	55 6 ± 14 8	10 6 ± 3 57
Coefficient of variation (%)	15 3	19 5	29 1	6 7
Extreme variations	78 3 153 5	92 9 197 9	131 0 280 4	143 1 169 0
Plasma volume (cc per Kg)				
Mean ± P E	39 3 ± 1 05	37 3 ± 0 70	45 0 ± 4 29	52 3 ± 6 50
Standard deviation ± P E	6 8 ± 0 74	4 3 ± 0 49	11 0 ± 3 03	13 6 ± 4 59
Coefficient of variation (%)	17 3	11 5	24 4	26 0
Extreme variations	27 3 52 3	19 1 - 49 1	27 9 57 3	35 9 65 3
Red cell volume (cc per Kg)				
Mean ± P E	76 0 ± 2 52	94 1 ± 3 89	145 3 ± 19 9	103 2 ± 1 72
Standard deviation ± P E	16 3 ± 1 78	23 8 ± 2 75	51 1 ± 14 0	3 6 ± 1 21
Coefficient of variation (%)	21 7	25 3	35 1	3 5
Extreme variations	43 3 109 8	64 3 156 1	86 8 227 5	98 1 106 1
Total Hemoglobin (Gm per Kg)				
Mean ± P E	25 1 ± 0 74	30 9 ± 1 03	46 7 ± 5 75	31 0 ± 0 42
Standard deviation ± P E	4 8 ± 0 63	6 4 ± 0 73	15 0 ± 4 13	0 9 ± 0 30
Coefficient of variation (%)	19 1	20 7	32 1	2 9
Extreme variations	14 7 36 7	22 1 51 2	28 6 70 1	29 8 33 3
Bilirubin (mg per 100 cc)				
Mean ± P E	2 30 ± 0 15	3 00 ± 0 28	2 30 ± 0 19	1 64 ± 0 30
Standard deviation ± P E	1 00 ± 0 11	1 71 ± 0 19	0 49 ± 0 13	0 64 ± 0 21
Coefficient of variation (%)	43 5	57 0	21 3	39 0
Extreme variations	1 00 4 13	0 91 - 7 24	1 76 2 88	0 74 2 21
Blood viscosity				
Mean ± P E	15 8 ± 0 83	20 7 ± 0 95	19 6 ± 2 56	18 6 ± 2 88
Standard deviation ± P E	5 4 ± 0 59	5 8 ± 0 67	7 6 ± 1 81	7 4 ± 2 03
Coefficient of variation (%)	34 2	28 0	38 8	44 6
Extreme variations	9 0 30 0	11 4 32 0	7 2 28 8	10 2 28 6

* Includes 1 patient with circulatory insufficiency

† Includes 2 patients with circulatory insufficiency

parallel changes in the erythropoiesis. We have investigated the gastric acidity of 9 patients with silicosis, all with pronounced polycythemia, employing a 7 per cent solution of alcohol and 1 cc of histamine phosphate (Parke, Davis & Company) as stimulants for the gastric mucosa (table 25). Free hydrochloric acid and pepsin were absent in all residual samples, in 5 cases free hydrochloric acid failed to appear after the ingestion of alcohol, and this condition persisted in 4 cases after injection of histamine. Previous observations, not published, made by one of us (A. H.) are related to these findings, of 37 native Indian residents of Morococha (at 4,540 meters, 14,900 feet) who were examined on account of various gastric symptoms (discom-

ation of the polycythemia which in some degree is found in most dwellers at high altitudes. The different aspects of this hematologic disorder, to which the names chronic mountain sickness, high altitude erythremia and Monge's disease have been given, have been recently reviewed by Monge.⁷⁴ Table 26 shows the hematologic characteristics and the degree of arterial oxygen saturation of 8 patients with this condition, whose cases have been described in greater detail in a recent paper.⁷⁵ When compared with the healthy residents of the altitudes at which they lived, all these patients showed a considerable increase in the hemoglobin and red cell volume, associated in most cases with a decrease in the plasma volume. The bilirubin was elevated in all the cases in which

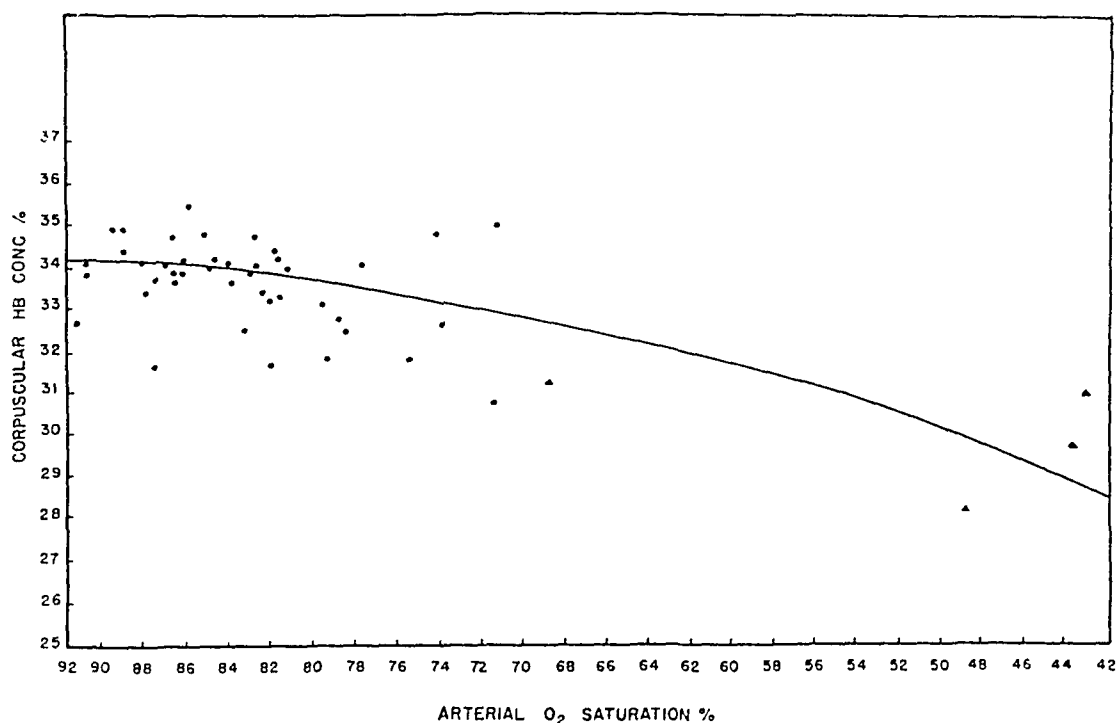


Chart 19—Relationship between the mean corpuscular hemoglobin concentration and the degree of arterial oxygen saturation in men with silicosis studied at high altitudes

fort, indigestion, etc.) an absence of free hydrochloric acid was verified in 21, equivalent to 56.7 per cent of the total. These results suggest that achlorhydria, and possibly achylia gastrica, is not an infrequent finding in residents of high altitudes, and that the polycythemia induced by the anoxic stimulus may coexist with this chemical change in the gastric contents. A similar observation has been made at sea level in a case of polycythemia vera.⁷²

Observations in Cases of Chronic Mountain Sickness—Monge,⁷³ in 1928, reported that loss of tolerance to a low barometric pressure environment after a constant or prolonged residence is frequently associated with an abnormal accentu-

ation of the polycythemia which in some degree is found in most dwellers at high altitudes. The leukocyte count was found to be within normal limits. These observations confirmed previous studies.⁷⁶ In all but 1 of the cases the arterial oxygen saturation was below the limits of variation found in healthy residents. Three of the 4 patients who were followed after descent to sea level had a decrease of the cell volume associated with a less proportional increase in the plasma volume.

In 3 cases of chronic mountain sickness in which the patients were studied after descent to sea level, Urteaga and Boisset⁷⁷ observed an

⁷⁴ Monge, C. *Physiol Rev* **23**:166, 1943.

⁷⁵ Hurtado, A. *Chronic Mountain Sickness*, J. A. M. A **120** 1278 (Dec 19) 1942.

⁷⁶ Hurtado, A. *Aspectos fisiologicos y patologicos de la vida en la altura*, Lima, Editorial Rimac, 1937.

⁷⁷ Urteaga, O., and Boisset, G. *An Fisiol*, Lima **25** 67, 1942.

⁷² Michaelidis, F. *Wien klin Wchnschr* **45** 1250, 1932.

⁷³ Monge, C., and others. *Cron med*, Lima **45** 238, 282 and 345, 1928, **46** 13, 58, 80 and 129, 1929.

increase in the hemoglobin and hematocrit values and in the total cell volume and a decrease in the plasma volume. The bilirubin content was elevated, and the test for excretion of this pigment revealed an abnormal retention. However, roentgen examination disclosed the presence of conditions, which may show analogous hematologic alterations on account of the increased anoxic stimulus present in both but which are two entirely separate entities, already has been emphasized,⁵⁵ and this is especially important in studies carried out in mining zones located at high altitudes.

TABLE 24—Leukocytes and Leukocytic Differential Counts of Patients with Silicosis with a High Degree of Anoxemia or Polycythemia (Observations Made at an Altitude of 3,730 Meters, 12,240 Feet)

Case No	Arterial O ₂ Saturation, %	Hemoglobin, Gm per 100 Cc	Hematocrit Reading, R B C, %	Leuko cytes, per Cu Mm	Neutro phils, Stab, %	Neutro phils, Segmented, %	Neutro phils, Total, %	Eosino phils, %	Baso phils, %	Mono cytes, %	Lympho cytes, %
1	43.3	22.72	72.1	8,720	28	60	88	0	0	4	8
2	48.9	20.82	74.1	6,280	7	76	8	0	1	5	11
3	43.9	17.66	58.5	5,360	20	66	86	1	0	4	9
4	71.2	28.68	82.3	5,680	8	65	73	1	2	10	13
5	68.8	21.77	69.6	5,200	20	68	88	0	0	4	8
6	71.4	25.00	81.2	6,460	1	65	66	0	0	9	25
7	75.3	23.07	72.6	5,280	9	71	80	2	0	2	15
8	83.2	24.04	65.4	5,960	14	39	53	3	1	9	34
9	86.1	23.10	68.2	6,000	16	52	68	4	0	3	25
10	79.5	25.30	76.5	6,760	4	71	75	1	0	7	17
11	78.1	24.78	73.0	5,880	14	64	78	0	0	4	18
12	82.1	26.42	81.1	7,600	8	65	73	1	1	9	16
13	82.4	24.93	76.9	6,400	10	63	73	1	0	2	24
14	90.8	23.92	68.6	7,880	4	71	75	1	1	1	22
15	78.3	24.22	75.0	7,500	2	65	67	2	3	5	23
16	83.2	25.85	78.8	4,720	11	47	58	2	0	6	34
17	78.8	25.38	77.2	11,200	7	19	56	7	2	3	32
18	78.2	26.69	81.2	5,600	4	46	50	2	0	5	45
19	86.5	24.45	71.6	7,600	8	48	56	5	0	8	31
20	87.8	26.64	80.1	5,660	5	46	51	2	0	3	44

TABLE 25—Gastric Acidity of Patients with Silicosis Studied at an Altitude of 3,730 Meters (12,240 Feet)

Case No	Arterial O ₂ Saturation, %	Hemoglobin, Gm per 100 Cc	Sample 1		Sample 2		Sample 3		Sample 4	
			Free HCl	Total Acid	Free HCl	Total Acid	Free HCl	Total Acid	Free HCl	Total Acid
			Cc of N/10 NaOH per 100 Cc							
1	85.4	23.79	0	10	13	26	15	32	22	36
2	83.1	24.05	0	5	0	10	4	4	3	16
3	79.2	22.87	0	9	0	5	0	7	0	8
4	82.9	27.47	0	12	20	32	32	40	34	42
5	70.8	24.01	0	3	0	4	0	4	0	4
6	77.7	26.28	0	8	0	10	0	10	0	8
7	87.4	20.15	0	6	0	8	10	18	16	24
8	78.2	23.98	0	4	0	6	0	8	0	10
9	89.6	22.55	18	30	16	24	24	34	28	46

Sample 1, residual
Sample 2, 20 minutes after 50 cc of 7 per cent alcohol
Sample 3, 40 minutes after 50 cc of 7 per cent alcohol
Sample 3, 15 minutes after injection of histamine

TABLE 26—Observations on Blood of Persons with Chronic Mountain Sickness

Case No	Place of Study, Altitude, Meters	Arterial O ₂ Saturation, %	Red Blood Cells, Millions per Cu Mm	Hematocrit, R B C, %	Hemoglobin, Gm per 100 Cc	Reticulo cytes, per Cent	Bilirubin, Mg per 100 Cc	Leuko cytes, per Cu Mm	Blood Volume, Cc per Kg	Plasma Volume, Cc per Kg	Red Cell Volume, Cc per Kg	Total Hemo globin, Gm per Kg
1	3,730	77.4	9.35	83.0	27.17	4.4	8.83	3,800	202.9	33.4	168.3	55.1
2	3,730	82.9	7.37	74.6	25.57	1.2	2.24	6,400	157.1	37.1	111.1	38.1
3	3,730	75.9	8.65	73.0	24.01	0.6	5.55	6,210	149.6	39.6	109.2	35.9
4	3,730	79.4	8.50	81.7	24.00	5.6	2.67	7,200	211.9	27.7	173.1	52.1
5	4,540	76.1	7.70	73.7	22.89	0.8	3.52	6,800	167.2	43.1	123.3	38.4
6	4,540	77.3	7.61	75.7	25.73	0.8		5,800	196.6	46.8	148.8	50.6
7	Sea level	95.9	8.00	79.2	26.13	0.3	4.59	6,100	186.2	37.8	147.3	48.6
8	Sea level	91.2	8.97	79.2	23.50	0		6,400	197.8	40.2	156.7	46.5

silicosis in 2 of the 3 subjects, so the reported findings in these cases may be related to this illness rather than to chronic mountain sickness. The importance of differentiating between these two

ROLE OF ANOXEMIA IN POLYCYTHEMIA OBSERVED AT SEA LEVEL

Polycythemia frequently accompanies chronic pulmonary diseases in which there is some degree

of arterial oxygen unsaturation. Such hematic alteration has been observed in subjects with fibrous changes in the lungs due to inhalation of dust,⁷⁸ with chronic bronchitis, asthma or emphysema,⁷⁹ with gas poisoning⁸⁰ and with primary pulmonary arteriosclerosis of unknown origin.⁸¹ The polycythemia which is found in association with Ayerza's disease, characterized by widespread fibrosclerotic pulmonary changes and right-sided heart failure,⁸² is well known. Our observations at high altitudes give further support to the generally accepted view that the polycythemia associated with such conditions represents a response to the anoxic stimulus. It is difficult, however, to establish a precise comparison between the polycythemia that develops at high altitudes and that observed with the dis-

we have constructed the diagram of chart 21 which shows the relationship between the degree of arterial oxygen unsaturation and the amount of circulating hemoglobin in cases of pulmonary fibrosis, emphysema and Ayerza's disease. It appears evident that most of the subjects with an arterial oxygen saturation of less than 90 per cent have some increase in hemoglobin, but this hematic response tends to be less than in residents of high altitudes with a corresponding degree of unsaturation and is frequently absent, especially in persons with pulmonary emphysema. The patients with Ayerza's disease have the highest increases in hemoglobin, of 18 studied by the investigators mentioned, 8, or 44.4 per cent, had values over 20 Gm per hundred cubic centimeters. The frequent lack of erythropoietic

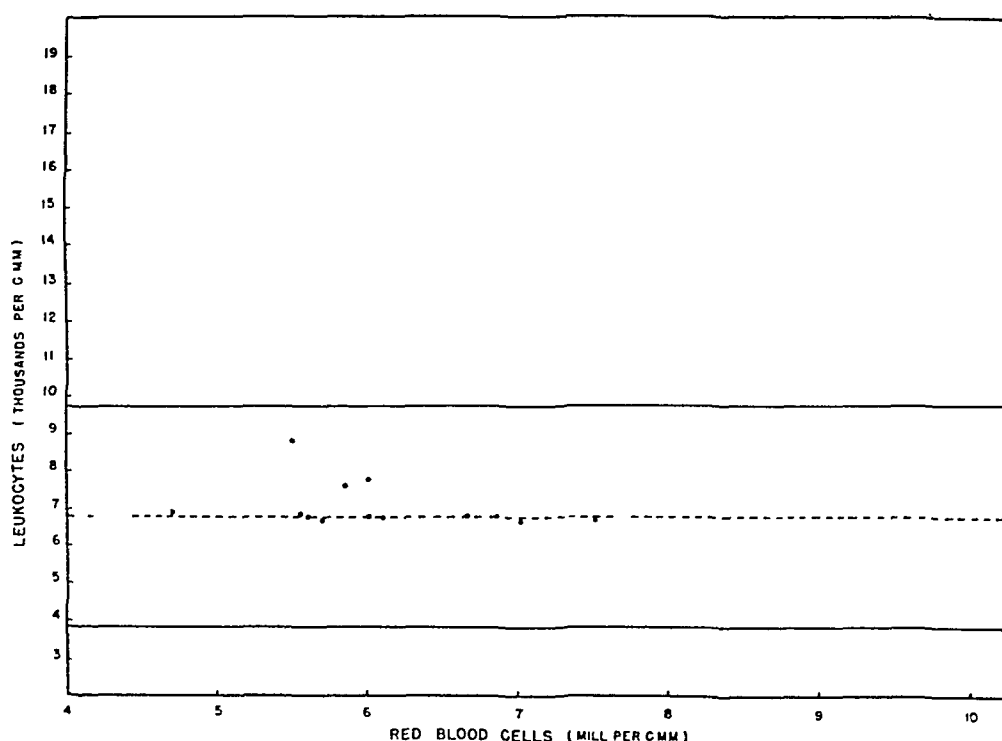


Chart 20—Leukocyte count in relation to the erythrocyte count in healthy and pathologic subjects studied at high altitudes. The zone between the horizontal lines represents the limits of variation observed in healthy men at sea level.

eases just mentioned, on account of the lack of information regarding the occurrence and the degree of anoxemia in most of the reported cases. From the data reported by Berconsky,⁸³ Capdehourat⁸⁴ and Hurtado, Kaltreider and McCann⁸⁵

response to the anoxemia which is usually associated with pulmonary emphysema has been previously pointed out.⁸⁴

The moderate degree of anoxemia, which has been found to be of common occurrence after the age of 60 years⁸⁵ not only fails to elicit a polycythemic response, but, according to recent observations,⁸⁶ is accompanied by low red cell counts and hemoglobin values.

78 Barker, N. W. Polycythemia Vera and Chronic Pulmonary Disease, *Arch Int Med* **47** 94 (Jan) 1931.
Kaltreider, Hurtado and Brooks.^{86g}

79 Waring, J. J., and Yegge, W. B. *Ann Int Med* **7** 190, 1933.

80 Barcroft, J., Hunt, G. H., and Dufton, D. *Quart J Med* **13** 179, 1920.

81 Darley, W., and Doan, C. A. *Am J M Sc* **191** 633, 1936.

82 (a) Berconsky, I. *Semana med* **1** 1569, 1933.
(b) Capdehourat, E. L. *La cianosis de los cardiacos negros de Ayerza*, Buenos Aires, Aniceto Lopez, 1934.
(c) Jimenez Diaz, C., Centenera, D., and Alemany, M. *Arch cardiol y hemat* **16** 306, 1935.

83 Hurtado, A., Kaltreider, N. L., and McCann, W. S. *J Clin Investigation* **14** 94, 1935.

84 Lemon, W. S. *Ann Int Med* **3** 430, 1929.
Kaltreider, Hurtado and Brooks.^{86g}

85 Dill, D. B., Graybiel, A., Hurtado, A., and Taquini, A. C. *Ztschr f Alterstorsch* **2** 20, 1940.

86 Newman, B., and Gitlow, S. *Am J M Sc* **205** 677, 1943.

There is rather scanty information in the literature regarding the blood volume and the morphologic characteristics of the erythrocytes in polycythemia secondary to pulmonary disease. It has been pointed out^{86d} that the increase in blood volume is moderate, however, values as high as 136 and 168 cc of blood per kilogram of body weight have been reported.^{36g} The investigation of the blood volume in cases of Ayerza's disease, in which the hemoglobin reaches the highest values observed with secondary polycythemia at sea level, will be of considerable interest. Kaltreider, Huitado and Brooks^{36f} found an unchanged corpuscular volume in cases of pulmonary fibrosis associated with some de-

polycythemia which has been frequently observed in cases of heart failure with a normal arterial oxygen saturation⁸⁷, an anoxia of the circulatory type is probably the main factor responsible for the bone marrow stimulation in these cases. Gibson and Evans⁸⁸ have found that the degree of increase in the blood volume in cases of circulatory insufficiency parallels the elevation of the venous blood pressure and the slowing of the circulation time. It is significant that increase in plasma volume such as was noted in their subjects at sea level has been observed by us at high altitudes in persons with silicosis associated with heart failure. A certain degree of polycythemia has been frequently observed in new-

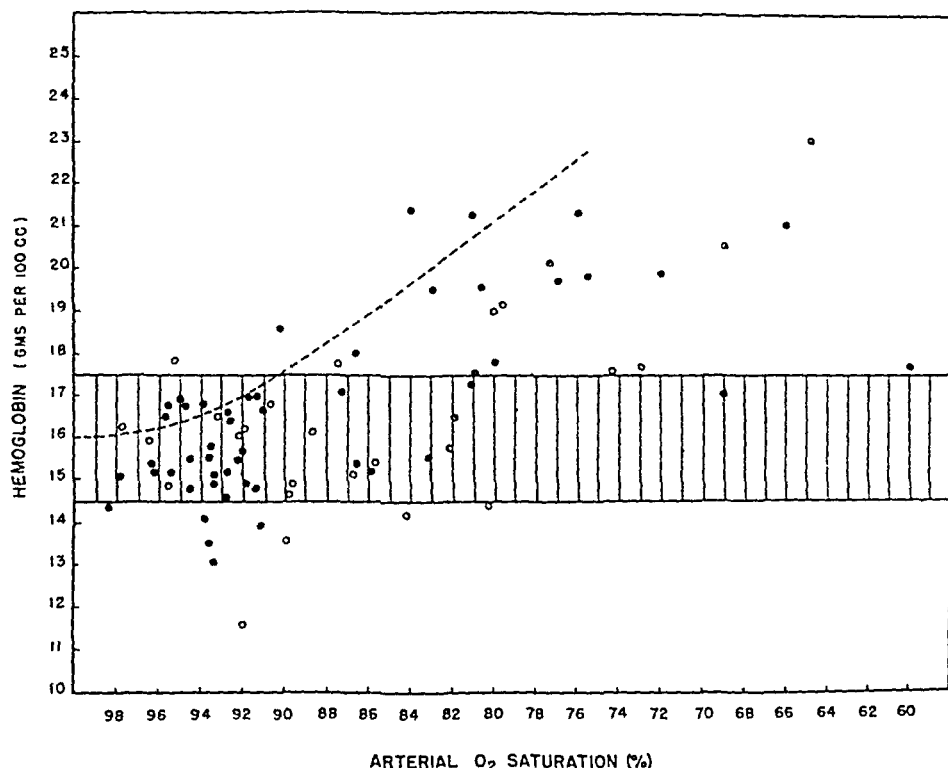


Chart 21—Relation between the hemoglobin content (grams per hundred cubic centimeters) and the degree of arterial oxygen saturation (per cent) in persons with fibrosis (solid dots), emphysema (open circles) and Ayerza's disease (dotted circles) studied at sea level. Data obtained from the literature⁸² and from previous investigations⁸³. The shaded area shows variations in the blood hemoglobin of healthy men living at sea level, the interrupted curve represents the approximate mean hemoglobin values which are found at various degrees of arterial oxygen saturation in healthy residents at high altitudes.

gree of polycythemia, but the size of the red blood cells had an inverse correlation with their number per cubic millimeter, with counts over 6,000,000 and 6,500,000 the mean corpuscular volume was found to be 81.4 and 74.3 cubic microns, respectively, figures which are distinctly lower than those found by us for residents of high altitudes with similar levels of polycythemia. An increase in the total mass of red cells with a reduction in the plasma volume, a finding similar to ours in the silicotic patients studied at high altitudes, has been recently reported by Hallock^{36h} in cases of congenital heart disease of the cyanotic type. Less clear appears to be the mechanism underlying the moderate

born infants,⁸⁹ and it is probably related, as has been suggested,⁹⁰ to the low oxygen saturation which has been demonstrated to exist during fetal life and at birth.⁹¹ The red blood cells of

87 Harrison, T. R. *Failure of the Circulation*, Baltimore, Williams & Wilkins Company, 1936. Altshule, M. D. *Medicine* **17** 75, 1938.

88 Gibson, J. G., and Evans, W. A. *J Clin Investigation* **16** 851, 1937.

89 Harrop, G., and Wintrobe, M. M. *Polycythemia in Downey, H. Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, vol. 4.

90 Goldbloom, A., and Gottlieb, R. *J Clin Investigation* **8** 375, 1930.

91 Barcroft, J., Kramer, K., and Millikan, T. A. *J Physiol* **90** 28P, 1937. Barcroft, J., and Mason, M. F. *ibid* **93** 32P, 1938.

newborn infants are larger and have a greater surface area than those of adults but the corpuscular hemoglobin concentration is identical with that of adults⁹²—morphologic characteristics which are similar to those observed by us in subjects constantly exposed to a low barometric pressure. The average corpuscular volume of 95 cubic microns found by Chumard, Osgood and Ellis^{92b} in a study of 195 newborn infants has a close similarity to the mean values of 95.2 ± 0.58 and 97.5 ± 0.75 cubic microns obtained for the Indian residents of Oroya (at 3,740 meters [12,240 feet] of altitude) and Morococha (at 4,540 meters [14,900 feet]) respectively. Wintrobe and Shumacker⁹³ have observed a high degree of macrocytosis associated with a low red cell count in the blood of fetuses. The high bilirubin content of the plasma in the newborn has been explained on the basis

associated with the chronic anoxemia of high altitudes.

Several investigations recently reviewed by Killick⁵⁰ have demonstrated the occurrence of polycythemia in human beings and animals with carbon monoxide anoxemia. The observations of Sayers, Yant, Levy and Fulton,⁹⁶ who found increases in the red blood cells and hemoglobin of men who had repeated daily exposures to carbon monoxide (contained in automobile exhaust gas), have a significance related to the polycythemia we have observed in men subject to the influence of intermittent periods of anoxemia at high altitudes. Some polycythemias produced experimentally in animals have been attributed to anoxic factors with a resulting stimulation of the erythropoietic activity. The polycythemia that follows the administration of cobalt, which is absolute in type,⁹⁷ seems to be

TABLE 27—*Level of Polycythemia, Reticulocytosis and Bilirubinemia in Relation to the Degree and Constancy of the Anoxemia (Summary of the Observations Made on Different Groups of Male Subjects)*

Groups	No of Sub jects	Altitude		Arterial O ₂ Saturation, %	Hemo globin, Gm per 100 Cc	Reticulo cytes, per Cent	Serum Bilirubin			Ratio D/T 100
		Meters	Feet				Mg. per 100 Cc			
							Total	Direct	Indirect	
Mean \pm P E										
I At sea level	175	0	0	96.1 \pm 0.12	16.00 \pm 0.04	0.5 \pm 0.02	0.72 \pm 0.02	0.57 \pm 0.01	0.35 \pm 0.01	51.4
II Temporary anoxemia										
(a) 2 hours' exposure	15	2,390	7,920	91.0 \pm 0.57	16.22 \pm 0.16	0.5 \pm 0.05	0.76 \pm 0.01	0.45 \pm 0.03	0.31 \pm 0.02	50.2
(b) 2 hours' exposure	16	3,140	10,300	89.6 \pm 0.74	16.31 \pm 0.15	0.5 \pm 0.08	0.67 \pm 0.04	0.36 \pm 0.02	0.31 \pm 0.01	53.7
(c) 2 hours' exposure	18	4,165	13,660	80.2 \pm 0.77	16.20 \pm 0.15	0.4 \pm 0.05	0.71 \pm 0.04	0.36 \pm 0.02	0.38 \pm 0.03	48.6
(d) 2 hours' exposure	18	4,835	15,870	75.3 \pm 0.93	16.53 \pm 0.18	0.4 \pm 0.04	0.79 \pm 0.07	0.39 \pm 0.03	0.40 \pm 0.01	49.4
III Intermittent anoxemia										
(a) Infrequent exposure *	60				16.53 \pm 0.09	0.7 \pm 0.05	1.00 \pm 0.06	0.45 \pm 0.02	0.56 \pm 0.05	43.0
(b) Daily exposure †	13				18.07 \pm 0.28	0.8 \pm 0.11	1.16 \pm 0.15	0.40 \pm 0.03	0.76 \pm 0.11	41.5
IV Chronic anoxemia										
(a) Native residents	40	3,730	12,240	87.6 \pm 0.27	18.82 \pm 0.15	0.8 \pm 0.06	1.47 \pm 0.09			
(b) Native residents	32	4,540	14,900	81.4 \pm 0.45	20.76 \pm 0.20	1.5 \pm 0.07	1.56 \pm 0.19	0.46 \pm 0.03	1.10 \pm 0.17	29.5

* Flight personnel (see text)

† Railroad personnel (see text)

of a high degree of destruction of blood⁹⁴ and of a decreased ability of the liver cells to excrete the pigment,⁹⁵ factors which must be also taken into consideration to explain the hyperbilirubinemia.

92 (a) Mugrage, E. R., and Andresen, M. I. Values for Red Blood Cells of Average Infants and Children, *Am J Dis Child* **51** 775 (April) 1936. (b) Chumard, E. G., Osgood, E. E., and Ellis, D. M. Hematologic Standards for Healthy Newborn Infants. Erythrocyte Count, Hemoglobin Content, Cell Volume, Color Index, Volume Index and Saturation Index, *Am J Dis Child* **62** 1188 (Dec) 1941.

93 Wintrobe, M. M., and Shumacker, H. B. *J Clin Investigation* **14** 837, 1935.

94 Gordon, M. B., and Kemellhor, M. C. *J Pediat* **2** 685, 1933. Rolleston, H., and McKee, J. W. *Diseases of the Liver*, London, The Macmillan Company, 1929. Ehrenfest, H. Causation of Intracranial Hemorrhages in New-Born, *Am J Dis Child* **26** 503 (Dec) 1923.

95 Snelling, C. J. *J Pediat* **2** 399, 1933. Waugh, T. R., Merchant, F. T., and Maughan, G. B. *Am J M Sc* **199** 9, 1940.

related to an interference with cellular respiration⁹⁸. The increases in the red cell count and hemoglobin produced by pressor drugs (epinephrine, ephedrine and amphetamine) have been explained on the basis of an abnormally low supply of oxygen to the bone marrow caused by a decrease in blood flow⁹⁹.

The most important polycythemic process at sea level is undoubtedly polycythemia vera, or 'Vasquez' disease, characterized by a considerable in-

96 Sayers, R. R., Yant, W. P., Levy, F., and Fulton, W. B. Effect of Repeated Daily Exposure on Several Hours to Small Amounts of Automobile Exhaust Gas, *Public Health Bulletin* 186, United States Treasury Department, Public Health Service, 1929.

97 Davis, J. E. *Proc Soc Exper Biol & Med* **45** 671, 1940.

98 Davis, J. E. *J Pharmacol & Exper Ther* **70** 408, 1940. Orten, J. M. *Detroit M News (Educ Issue)* **32** 42, 1941.

99 Davis, J. E. *Am J Physiol* **133** 258, 1941, **134** 219, 1941.

crease in the circulating blood volume. The cause of this disease is unknown, but among the various theories which have been advanced those related to the possible existence of an anoxic stimulating factor have a prominent place. All investigators¹⁰⁰ have reported normal values for the oxygen saturation of the arterial blood, but Harrop and Heath¹⁰¹ found a reduction following exercise, which they attributed to a decreased permeability of the alveolar membrane for the passage of oxygen, to the anoxemia thus produced a causative significance was attributed. Reznikoff, Foot and Bethea¹⁰² have found in cases of this disease a marked thickening of the capillaries and fibrosis of the arterioles in the bone marrow, changes which have led them to propose the theory that the erythremia may be due to a local oxygen deficiency in the erythropoietic organs, with overcompensation of erythropoiesis. Hallock,¹⁰³ from observations related to the production of lactic acid during exercise, suggested that tissue anoxia may be an important causative factor of polycythemia vera.

The increase in the circulating blood volume due to a greater mass of red cells with a practically unchanged or decreased plasma volume, is a characteristic common to the polycythemia observed at high altitudes and polycythemia vera. However, a comparative study of the results obtained by several investigators¹⁰⁴ in the study of a total of 91 subjects (males) with the latter disease and our findings in 97 healthy residents and persons with silicosis at high altitudes reveals that the increase in blood volume is more pronounced and has a greater range of variation in the patients with polycythemia vera (chart 22). The mean value for all reviewed cases of this disease was 154.1 ± 2.73 cc of blood per kilogram of body weight, with a standard deviation of 38.5 cc, while in the 97 of polycythemia at high altitudes the mean volume was 120.6 ± 1.72 with a standard deviation of 25.1 cc.

100 Altschule, M. D., Volk, M. C., and Henstell, H. *Am J M Sc* **200** 478, 1940.

101 Harrop, G. A., and Heath, E. H. *J Clin Investigation* **4** 53, 1927.

102 Reznikoff, P., Foot, N. C., and Bethea, J. M. *Am J M Sc* **189** 753, 1935.

103 Hallock, P. *Proc Soc Exper Biol & Med* **38** 587, 1938.

104 Haden, R. L. *Am J M Sc* **196** 493, 1938. Sohval, A. R. *Hepatic Complications in Polycythemia Vera, with Particular Reference to Thrombosis of Hepatic and Portal Veins and Hepatic Cirrhosis*, *Arch Int Med* **62** 925 (Dec) 1938. Gibson, J. G., Harris, A. W., and Swigert, V. W. *J Clin Investigation* **18** 621, 1939. Meyer, O. O., and Thewlis, E. W. *J Lab & Clin Med* **26** 1137, 1941. Rountree and Brown^{36a} Goldbloom and Libin^{36b} Hallock^{36c} Altschule and others¹⁰⁰

There are certain other comparative aspects which have interest from the point of view of the etiologic mechanisms responsible for the polycythemic processes in these two groups of cases. A statistical analysis of the data published by Rountree and Brown, Brown and Giffin¹⁰⁵ and Brown and Roth,¹⁰⁶ which refer to observations made on a total of 62 male patients with polycythemia vera, gives mean values of 22.56 ± 0.30 Gm of hemoglobin per hundred cubic centimeters and 63.7 ± 0.61 red cells per cent for the hematocrit value. According to our observations, these mean values would correspond, approximately, to those found in men living at an altitude of 5,300 meters (17,400 feet) with an arterial oxygen saturation of about 76.0 per cent.

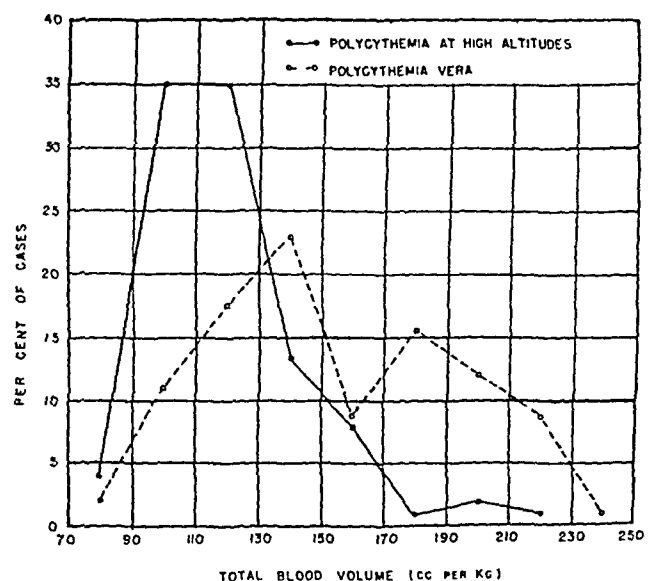


Chart 22—Variations in blood volume (expressed in cubic centimeters per kilogram of body weight) in 97 healthy and pathologic subjects studied at high altitudes (with arterial oxygen saturations ranging from 43.3 to 90.2 per cent) and in 91 persons with polycythemia vera observed at sea level. The data corresponding to the latter disease have been collected from the literature¹⁰⁷.

The size of the red blood cells has been found to be normal or moderately decreased in most cases of polycythemia vera,⁸⁹ and microcytes are often observed¹⁰⁷, in the series of 62 cases to which we have just referred, the mean corpuscular volume and hemoglobin concentration were found to be 92.2 ± 0.94 cubic microns and 36.4 ± 0.24 per cent, respectively. These figures are not unlike those found by us in polycythemia of high altitudes, but it appears that in the latter process there is a deviation toward

105 Brown, G. E., and Giffin, H. Z. *Treatment of Polycythemia Vera (Erythremia) with Phenylhydrazine*, *Arch Int Med* **38** 321 (Sept) 1926.

106 Brown, G. E., and Roth, G. M. *J Clin Investigation* **6** 159, 1928.

107 Schalm, L. *Folia haemat* **63** 34, 1939. Wintrobe²⁰

a slight macrocytosis which is not observed in polycythemia vera. Nucleated red cells in the peripheral blood are not infrequently noted in this disease,¹⁰⁸ a finding not verified by us in the case of any subject studied at high altitudes, regardless of the degree of anoxemia and the level of polycythemia. The increase in the serum bilirubin seems to be more intense and frequent in polycythemia of high altitudes, as may be judged from the comparison of our data with those contained in recent monographs on polycythemia vera.⁹⁹

Another distinction, which is probably the most important and of fundamental significance, relates to the great frequency of leukocytosis and leukemia, with appearance of immature white cells in the peripheral blood, in cases of polycythemia vera; this characteristic has been emphasized by all writers. With the exception of a moderate and temporary leukocytosis which is observed at times during the early period of exposure to a low barometric pressure and probably is due to factors of mobilization and release, there is no disturbance of the leukoblastic activity in the polycythemia of high altitudes, no matter how intense and constant are the anoxic stimulus and the degree of erythropoietic response. Finally, an important clinical distinction is the absence of splenomegaly in healthy and in diseased polycythemic subjects living at high altitudes, in contrast with its frequency in persons with polycythemia vera, according to a recent study¹⁰⁹ the increased size of the spleen was clinically verified in about 66 per cent of 163 cases of the latter disease. A somewhat closer similarity with the polycythemia of healthy persons living at high altitudes is found in the so-called familial polycythemia, in which the increase in the total cell volume is associated with an unchanged or moderately decreased plasma volume, normal morphologic characteristics of the red cells and absence of leukocytosis and changes in the leukocytic differential count.¹¹⁰ The small number of persons with this disease studied and the lack of observations concerning the degree of arterial oxygen saturation prevent, however, an adequate comparative study.

COMMENT

Attention has been called by many investigators to the wide individual variations observed in the hematologic response to the anoxemia associated with exposure to a low pressure environment.

108 Minot, G. R., and Buckman, T. E. *Am. J. M. Sc.* **166**:469, 1923. Harrop and Wintrobe.⁵⁹

109 Tinney, W. S., Hall, B. E., and Giffin, H. Z. *Proc. Staff Meet., Mayo Clin.* **18**:46, 1943.

110 Nadler, S. B., and Cohn, I. *Am. J. M. Sc.* **198**:41, 1939.

This characteristic has also been noted in the present study, however, an analysis of the collected data indicates that in general the level of polycythemia, together with the signs of erythropoietic hyperactivity and increased amounts of serum bilirubin, are related to the degree, duration and continuity of the anoxic stimulus and that the variability affects chiefly the early phase of the response (table 27). When the period of anoxemia is short of a few hours' duration, the increase in red blood cells and hemoglobin is not a constant phenomenon and, when it occurs, shows the individual variations which have been repeatedly emphasized. On the other hand, when the anoxemia is permanent, there is found in a large majority of cases of polycythemia the level of which is closely related to the degree of anoxic stimulus. Intermittent exposure to anoxemia occupies an intermediate position from the point of view of the hematologic response, the occurrence of polycythemia and its level, though there are large variations in the latter, are also broadly related to the frequency and intensity of the anoxic stimulus.

It appears that in the presence of an anoxic condition the release of stored red blood cells is a labile and variable emergency mechanism of adaptation, the late response based on an increased production of cells by a hyperactive bone marrow, is a more constant adaptative process. Many of the apparently contradictory results obtained in hematologic studies made at high altitudes and in low pressure chambers seem to be related to different experimental conditions in regard to the duration of the exposure and the level of altitude, or simulated altitude, reached.

The more or less definite inverse relationship which exists between the level of polycythemia and the degree of arterial oxygen saturation in dwellers at high altitudes, corroborates the opinion advanced by Bert¹, Viault² and Miescher¹¹¹ in the latter part of the last century, and accepted by most investigators, that the deficient oxygen supply to the bone marrow is the main stimulus for the increased production of red blood cells and hemoglobin. The fact that at the same altitude the polycythemia is more pronounced in men with a higher degree of arterial oxygen unsaturation (as in the subjects with silicosis studied by us) indicates that environmental factors, such as increased solar radiation, do not play a fundamental role in the causative mechanism of the hematic response as was suggested by Kestner¹¹². While it has been generally accepted that at high altitudes and in other similar conditions the low tension of the oxygen

111 Miescher, F. *Cor-Bull. Schweiz. Anst.* **23**:809, 1893.

112 Kestner, O. *Ztschr. f. Biol.* **73**:1, 1922.

physically dissolved in the plasma constitutes the immediate stimulus for the erythropoietic hyperactivity, the relative importance of other factors, such as the percentage of hemoglobin saturation and the absolute concentrations of reduced and oxygenated hemoglobin, remain yet to be adequately understood, in anemic anoxia, clinical or experimentally produced, in which the blood oxygen tension is normal, a relationship has been noted to exist between the degree of erythropoietic hyperactivity and the level of anemia.¹¹³ There seems to be a limit for the anoxic factor in the stimulation of the erythropoietic activity, when the arterial oxygen saturation reaches a value of about 60 to 70 per cent, there is a decrease, rather than a further increase, in the hemoglobin and red cell count. This suggests that the hematologic compensatory adjustment ceases to be effective at a degree of anoxemia which corresponds, roughly to an altitude of 6,000 meters, or 20,000 feet, above this level the proportion of reduced over oxygenated hemoglobin increases rapidly. This limit in the polycythemic response does not appear to be related to an anatomic limitation of the erythropoietic organs, because no plateau, or flattening, is observed in the curve representing the level of polycythemia with increasing degrees of anoxemia. It may be associated with a higher rate of destruction of cells, as has been suggested by Talbott⁵⁶, the accentuation of reticulocytosis, which has been observed to occur with a high degree of anoxemia would favor this interpretation, but on the other hand this is not accompanied with an increased accumulation of bilirubin in the plasma. According to our observations, an increasing degree of anoxemia has a tendency to lower the hemoglobin concentration of the circulating erythrocytes, this fact makes it seem possible that an interference with the production of hemoglobin rather than with the building of the erythrocytic stroma is responsible for the lack of an appropriate polycythemic response to severe degrees of anoxemia.

From the observations made in men constantly exposed to a low barometric pressure it appears that the level of hemoglobin in the circulating blood can be regarded as one of the many factors which tend to preserve the internal stability or homeostasis, as it has been called by Cannon,¹¹⁴ against the disturbing influence of a low oxygen tension in the inspired air, it increases, up to a certain limit, in relation to the degree of disturbance in the external environment and

decreases when normal conditions are restored. It is interesting to observe that chronic anoxemia, even when present since birth, does not modify permanently the activity of the erythropoietic organs. When the native of high altitudes comes down to sea level his blood acquires, after a certain time, the same morphologic characteristics as those found in persons who were born and have lived at sea level. This fact eliminates the possibility that racial factors play a part in the development of polycythemia at high altitudes. The frequent moderate reduction in red blood cells and hemoglobin, which has been observed in men born at high altitudes during their first few months of residency at sea level may be related to an adaptative period on the part of the bone marrow to the disappearance of the potent anoxic stimulus present at high altitudes. These findings are not unlike those of Gordon and Kleimberg,¹¹⁵ who observed in animals a moderate process of anemia after cessation of exposure to a low pressure in a chamber.

The polycythemia of high altitudes, which has been classified as an erythrocytosis, is, according to this and previous studies, absolute in type. An increase in the circulating blood volume, due to a larger cell mass with an unchanged or decreased plasma volume, has been observed in persons who have just arrived at high altitudes and in healthy and in diseased human beings and animals living permanently in such environment. The increase tends to be proportional to the level of altitude and the degree of anoxemia, often reaching high values. It appears that there must be a modification of the following concept, advanced about fifteen years ago^{36d} and still found in the literature: "Increases in blood volume to 115 or 120 cubic centimeters for each kilogram of body weight, rarely or never occur as responses of the blood to lowered oxygen tension." A slight macrocytosis is another characteristic of the polycythemia related to a constant exposure to a low barometric pressure. The increased size of the red blood cells may be due, in part, to the erythropoietic hyperactivity¹¹⁶ and to the presence of an excess of reticulocytes, cells which have been found to have a large volume.¹¹⁷ Whether this morphologic variation, which includes a greater corpuscular surface area, represents a compensatory adjustment on the part of the circulating respiratory unit for the acquisition and transport of the oxygen is an interesting possibility. The stimulating influence of the anoxemia caused by a low oxygen tension in

113 Robschert-Robbins, F. S., and Whipple, G. H. *Am J Physiol* **134** 263, 1941. Hurtado, Pons and Merino.¹⁹

114 Cannon, W. B. *Physiological Regulation of Normal States. Some Tentative Postulates Concerning Biological Homeostatics*, in Jubilee Volume for Charles Richet, Paris, 1926, p. 91.

115 Gordon, A. S., and Kleimberg, W. *Proc Soc Exper Biol & Med* **37** 507, 1937.

116 Haden, R. L. *J Lab & Clin Med* **22** 439, 1937.

117 Cruz, W. Q. *Am J M Sc* **202** 781, 1941.

the inspired air is restricted to the processes concerned with the production of red blood cells and hemoglobin. Leukogenetic activity remains undisturbed even in persons who have a high level of polycythemia and a severe degree of anoxemia. Only during the early period of exposure to a low barometric pressure is observed, occasionally and with more frequency at the higher altitudes, a moderate and temporary leukocytosis, probably related to factors of mobilization and release. The tendency for an inversion in the leukocytic formula, with a relative increase in the lymphocytes and a proportional reduction in the other cells, observed in dwellers at high altitudes, even at relatively low elevations, has been ascribed to the action of a more intense solar radiation.¹¹⁸

The polycythemia which occurs under the influence of a temporary anoxemia, such as the one observed on persons' arrival at high altitudes, seems to be in most cases the combined result of release or mobilization of stored blood and a process of hemoconcentration. The comparative study of the values for blood volume determined for the same subject within the first two hours after his arrival at high altitudes and a few days previously is open to criticism on account of the possible physiologic variations which might have taken place during the interval, but the constancy of the results obtained suggests, however, that the mechanisms mentioned play a part in the observed polycythemia. The existence of reserves of blood in man, almost universally accepted since the classic experimental work of Barcroft¹¹⁹ and others on the role of the spleen, has been recently denied by Ebert and Stead,¹²⁰ who investigated the hematic response to exercise, epinephrine and hemorrhage, employing the blood volume method of Gibson and Evans.¹⁵ But the observations of Kaltreider, Meneely and Allen¹²¹ on the effect of epinephrine on the volume of blood and those of Glickman and others¹²² concerning the effect of hot environmental conditions, made by the same dye method, and the recent studies of Watson and Paine,¹²³ who analyzed the blood obtained directly from the splenic vein after the injection of epinephrine into the splenic artery,

give fairly good evidence that reserves of blood do exist in the body.

The polycythemia of chronic anoxemia corresponds to an increased erythropoietic activity as evidenced by the excess of reticulocytes found in the peripheral blood. This reticulocytosis which is more pronounced the higher the altitude and the degree of anoxemia, cannot be explained simply on the basis of a greater number of red blood cells per cubic millimeter; it is a qualitative as well as a quantitative process, and of a given number of erythrocytes expelled by the bone marrow a higher proportion are immature at high altitudes than at sea level. The absence of nucleated red cells in the peripheral blood suggests that the increased erythropoietic activity proceeds in a somewhat orderly fashion.

A definite elevation of the serum bilirubin, due almost entirely to an increase in the indirect fraction, is another fairly constant finding in men exposed frequently or permanently to a low barometric pressure. There are wide individual variations, but in general the increase in the pigment is directly proportional to the level of polycythemia (table 27), which suggests that a greater rate of cellular destruction, which corresponds, in turn, to an increased rate of formation, is an important factor in the mechanism causing the hyperbilirubinemia. Whether the normal liver cells should be able to excrete all the pigment, regardless of its rate and amount of formation, is still an unsettled question among students of hepatic physiology. There are other factors present at high altitudes which may decrease the efficiency of this organ in its excretory function. The well known investigations of Rich,¹²⁴ who observed that rats placed in low oxygen tension chambers showed a diminished ability to excrete intravenously injected bilirubin and had degenerative changes in the liver cells, and the similar findings of Campbell,¹²⁵ in regard to organic changes that developed in other animals placed under similar experimental conditions, suggest that anoxemia per se when prolonged or constantly present may be an important factor in causing hepatic insufficiency from the point of view of excretion of pigment. Our findings of a proportional relationship between (1) the level of hyperbilirubinemia and the degree and duration of the anoxemia and (2) the abnormal retention of injected bilirubin in native residents of high altitudes are in favor of that possibility. The increase in the circulating blood volume, a characteristic of the polycythemia of high altitudes, may play an additional role in the

118 Kennedy, W. P., and Mackay, J. J. *Physiol* **87** 337, 1936.

119 Barcroft, J. *Lancet* **1** 319, 1925.

120 Ebert, R. V., and Stead, E. A. *Am J M Sc* **201** 665, 1941.

121 Kaltreider, N. L., Meneely, R., and Allen, I. D. *J Clin Investigation* **21** 339, 1942.

122 Glickman, N., Hick, F. K., Keeton, R. W., and Montgomery, M. M. *Am J Physiol* **134** 165, 1941.

123 Watson, C. J., and Paine, I. R. *Am J M Sc* **205** 493, 1943.

124 Rich, A. R. *Bull Johns Hopkins Hosp* **47** 338, 1930.

125 Campbell, J. A. *Lancet* **2** 84, 1928.

etiologic mechanism of the hyperbilirubinemia, according to recent studies made in cases of polycythemia vera by Tinney, Hall and Giffin,¹⁰⁹ these investigators found hepatic complications in 25 per cent of 163 cases of the latter disease, and suggested that these may be due to several factors, among which they mentioned distention of the portal circulation in the liver, stasis caused by increased viscosity of the blood and impairment of the nutrition of the hepatic cells as a result of the circulatory alterations. Urteaga¹²⁶ has suggested that a raised threshold of the hepatic cells for excretion of bilirubin may be present at high altitudes. Further studies are necessary for the final elucidation of the problem, but it appears likely at the present time that the hyperbilirubinemia present in most persons exposed frequently or constantly to a high altitude is the combined effect of several factors, among which an increased rate of pigment formation and a decreased power of the hepatic cells to excrete pigment, due to the anoxemia, are probably the most important. Another aspect, related to the possible increased rate of cellular destruction present at high altitudes, is the possibility that the products derived from the red cell disintegration will serve as an additional stimulus for increased formation, as has been observed experimentally.¹²⁷ If so the person subjected to the influence of chronic anoxemia would be placed in a sort of a vicious circle in regard to erythropoietic activity.

The effectiveness which the polycythemia of high altitudes has as a compensatory process is still a debated question. There is abundant evidence to show that the development of symptoms associated with exposure to a condition of temporary anoxemia and the degree of acclimatization found in men living permanently at high altitudes cannot be strictly rated in terms of polycythemic levels. The understanding of these aspects becomes clearer if one realizes that the essential problem at high altitudes is not limited to the amount of oxygen carried in the blood, as a matter of fact, as it was originally pointed out by Barcroft and others,³ the resident at a high altitude has in his arterial blood a higher oxygen content than the person living at sea level. The chief difficulty lies in the reduced tension of the small fraction of gas physically dissolved in the plasma, which represents the immediate source of supply to the tissues, a high hemoglobin concentration with a high oxygen content in the circulating blood, although decreasing, in part, the effects of the reduced

tension, is not, in consequence, incompatible with all the limitations which an exposure to a low barometric pressure brings to the body. A significant observation has been recently made by Dorrance and others¹²⁸; these investigators observed that the polycythemia caused by the administration of cobalt to rats increased the work performance of these animals under conditions of anoxia. The resident of high altitudes has been almost exclusively studied at rest, his capacity for graded physical activity and the relative importance of his various organic and functional characteristics in the adaptation to the increased demands of work are practically unknown.

Further studies concerning muscle hemoglobin, which has been found to be increased in dogs living at high altitudes¹²⁹ but has not yet been investigated in human beings, will be of considerable interest from the point of view of acclimatization. Owing to its peculiar characteristics in regard to the affinity and combination with oxygen,¹³⁰ this substance may play an important role in compensatory adjustment to a deficient oxygen supply, as has been already suggested.¹³¹

The study of the hematologic observations made by several investigators at sea level on persons with some degree of arterial oxygen unsaturation due to pulmonary disease shows that the polycythemic response in them was less constant and in general less pronounced than that observed by us in men living at high altitudes with a similar degree of anoxemia, except in cases of Ayerza's disease. No adequate explanation can be given at the present time for this difference. The lack of polycythemia is especially frequent in cases of pulmonary emphysema, in spite of the almost constant anoxemia present in this disease. It suggests that, in addition to the fundamental anoxic stimulus, some other factors, perhaps associated with the nature of the pulmonary lesions, circulatory abnormalities, reflex mechanism, etc. may play some secondary role in bringing on the erythropoietic hyperactivity. It is interesting in this respect that the persons with Ayerza's disease, in whom the associated polycythemia usually reaches high values, have clinical and hematologic characteristics (appearance of the roentgenograms of the lungs, abnormal lowering of the arterial oxygen

128 Dorrance, S. S., Thorn, G. W., Clinton, M., Edmonds, H. W., and Faiber, S. *Am J Physiol* **139** 399, 1943.

129 Hurtado, A., Rotta, A., Merino, C., and Pons, J. *Am J M Sc* **194** 708, 1937.

130 Millikan, G. A. *J Physiol* **87** 38P, 1936.

131 Hill, R. *Proc Roy Soc, London, s B* **120** 472, 1936.

126 Urteaga, O. *An Fac de med, Lima* **25** 89, 1942.

127 Boycott, A. E., and Oakley, C. L. *J Path & Bact* **36** 205, 1933.

saturation, right-sided heart failure, etc.) similar to those of patients with chronic mountain sickness, who at high altitudes show an abnormal accentuation of the polycythemia.⁷⁵

An increase in the circulating blood volume is a common finding in the polycythemia of high altitudes and in polycythemia vera, but a comparative study of these processes raises a strong argument against the acceptance of the theory that an anoxic stimulus plays a significant role in the development of the latter disease. The increase in the red cell volume tends to be greater in polycythemia vera, which also lacks the proportional relationship between the level of polycythemia and the signs of increased red cell formation and destruction observed in men exposed constantly to a low oxygen tension. The absence of nucleated red cells in the peripheral blood (a not infrequent finding in polycythemia vera) at high altitudes, regardless of the degree of anoxemia and the level of polycythemia, and, of fundamental importance, the lack of disturbance in the leukogenetic activity indicates that the hematologic response to anoxia does not show a disorder of the entire hemopoietic system, such as occurs often in polycythemia vera. An apparently greater similarity, from the point of view of the increase in the circulating blood volume, is found between this disease and chronic mountain sickness, but the fundamental differences, in the characteristics of the bone marrow activity and the involvement of the leukocytes are also evident in these processes. In addition, there is some evidence that the hematologic alterations in chronic mountain sickness are related to pulmonary factors not present in polycythemia vera.⁷⁵

SUMMARY AND CONCLUSIONS

Investigations have been made, at sea level and at high altitudes, in several series of healthy and diseased male subjects, concerning the influence of temporary, intermittent and chronic anoxic anoxia (anoxemia) on the morphologic and other characteristics of the circulating blood. The related literature has been briefly reviewed. The main observations lead to the following conclusions:

1 Exposure to a low barometric pressure environment causes in most cases a polycythemic response. There are wide individual variations but in general the level of polycythemia is directly proportional to the degree, duration and continuity of the anoxic stimulus.

2 There seems to be a limit for the hematologic response to the anoxic stimulus. When this is extremely severe a decrease rather than a further increase is observed in the resulting polycythemia. An interference with the forma-

tion of hemoglobin may be the responsible mechanism.

3 The level of hemoglobin in the circulating blood may be considered as one of the many factors which tend to preserve the internal stability or homeostasis, against the disturbing influence of a constant lowering of the oxygen tension in the inspired air.

4 The polycythemia associated with the anoxemia of high altitudes is absolute in type. The elevation in the total blood volume, which at times reaches high values, is due to an increased red cell volume.

5 The polycythemia observed on persons arrival at high altitudes seems to be due to factors of release of stored blood and hemoconcentration, that corresponding to a repeated or constant exposure to a low pressure environment is related to an erythropoietic hyperactivity.

6 The polycythemia associated with a constant or intermittent anoxemia tends to show a proportional elevation in the circulating reticulocytes and in the serum bilirubin. The latter characteristic suggests that an increased rate of cellular destruction parallels the increased formation but other factors, such as insufficiency of the liver in excretion of pigment, due to the anoxic condition, may also play an etiologic role in the observed hyperbilirubinemia.

7 The stimulating influence of anoxemia on the hemopoietic system is restricted to the formation of red blood cells and hemoglobin. Leukopoietic activity is not affected, and the moderate and temporary leukocytosis which at times is observed on a person's arrival at a high altitude is probably related to the release and mobilization of stored blood.

8 Chronic anoxemia does not modify the erythropoietic activity permanently. When a person who has lived since birth at high altitudes is brought down to sea level, he shows after some time blood characteristics similar to those found in persons who have always lived under the latter environmental conditions. During the early period of adaptation to the normal pressure environment there frequently occurs an abnormal decrease in the red blood cells and hemoglobin.

9 Comparative study of the polycythemia of high altitudes and the polycythemic processes observed at sea level indicates that (a) in cases of anoxemia at sea level due to pulmonary changes the polycythemic response tends to be less than with corresponding degrees of arterial oxygen unsaturation at high altitudes except in cases of Ayerza's disease. (b) it is not likely that the causative mechanism of polycythemia vera is related to the existence of an anoxic stimulus.

EFFECTS OF SOME LIVER EXTRACTS ON THE CARBOHYDRATE METABOLISM

HENRY B. SOKAL, M.D.

PROOFLIN

The nineteen-twenties will go down in medical history as the decade of two great therapeutic discoveries. Barely four years had elapsed since Banting's epochal discovery of insulin when Minot and Murphy¹ startled the world by their announcement of the effect of liver on the course of pernicious anemia. The groundwork for this discovery was laid earlier by the studies of Whipple and his associates² on the effect of a diet rich in red meat and liver on erythropoietic activity in dogs with experimentally produced anemia.

The next important step in the progress of liver therapy was the preparation of an active liver extract which could be administered either by mouth or parenterally. This overcame the objections of many patients to the monotony of a daily diet including liver.

With the value of liver therapy firmly established, two questions occupied the minds of investigators: 1. What is the nature of the anti-anemia principle present in the liver? 2. What side effects, if any, do liver or liver preparations have on other functions of the body? This paper is concerned only with the second question.

That liver and liver extract influenced the carbohydrate metabolism was claimed long before the discovery of insulin and the introduction of liver as a specific treatment for pernicious anemia. At the end of the nineteenth century French clinicians advocated the use of liver and of liver extracts in the treatment of diabetes mellitus. The results, however, were not uniform. Sometimes the administration of liver or of liver extract was followed by a remarkable improvement. The glycosuria seemed to be diminishing or disappeared entirely, and the patient felt better. At other times liver had no effect on the course of the disease, on the contrary, the diabetic symptoms increased in severity, with a corresponding increase in the urinary concentration of dextrose.

1 Minot, G. R., and Murphy, W. P. Treatment of Pernicious Anemia by Special Diet, *J. A. M. A.* **87** 470 (Aug 14) 1926.

2 Whipple, G. H., and Robschert-Robbins, F. S. *Am. J. Physiol.* **72** 408, 1925.

To explain these divergent results obtained with liver therapy Gilbert and Carnot³ assumed that a diabetic patient might suffer from either hyperfunction or hypofunction of the liver. Thus, they reasoned, a person with diabetes and a hypofunctioning liver will ultimately benefit from the liver diet, while a patient with a hyperfunctioning liver will get worse. In their conclusion they went one step further, advocating the use of a liver diet as a test of the functional activity of the liver in the diabetic person. Other French clinicians published similar reports on the effect of liver in diabetes. Even as late as 1921, attempts were still being made to treat diabetes with liver extract. In that year Levin,⁴ in an article entitled "My Observations With Hepatic Extract As a Remedial Agent," related the good results he obtained with a specially prepared soluble liver extract in 4 diabetic patients. With the introduction of insulin as a standard treatment of diabetes these experiments were abandoned.

The publication of an article by Blotner and Murphy⁵ in which they claimed for liver an insulin-like action on the blood sugar concentration both in diabetic and in nondiabetic persons brought the whole question of the effect of liver on the carbohydrate metabolism back into the limelight. In a second paper⁶ they described the results obtained from the administration of a specially prepared liver extract in 19 diabetic patients. Their conclusions were similar to those already reported, namely, that their liver extract contained a sugar-reducing substance, which was active when taken by mouth, was nontoxic and had an effect on the blood sugar concentration similar to that obtained with small doses of insulin. A similar report was published by Lombardi.⁷ On the other hand, Brett and

3 Gilbert and Carnot. *Gaz. d. hop.* **73** 995, 1900.

4 Levin, A. L. *South. M. J.* **15** 175, 1922.

5 Blotner, H., and Murphy, W. P. Effect of Liver on Blood Sugar Level, *J. A. M. A.* **92** 1332 (April 20) 1929.

6 Blotner, H., and Murphy, W. P. Effect of Certain Liver Extracts on Blood Sugar of Diabetic Patients, *J. A. M. A.* **94** 1811 (June 7) 1930.

7 Lombardi, E. *Riforma med.* **46** 7, 1930.

his associates,⁸ working with a liver extract carefully prepared according to the recommendations of Blotner and Murphy, not only failed to substantiate these claims but, on the contrary, noticed a slight rise in the blood sugar concentration following the administration of the liver extract

An interesting report on the comparative effects of liver and of liver extract in pernicious anemia and diabetes, in one of those rare cases in which the patient suffered from both diseases, was made by Bowen⁹. Bowen's patient, a man 55 years old, was found to have pernicious anemia in 1928. He was then treated with raw liver and liver extract. In March 1929 he began to show symptoms of diabetes. He was therefore given insulin for the diabetes in addition to whole liver for the anemia. During this period the amount of insulin had to be reduced on account of the ensuing hypoglycemia. At this stage liver extract was substituted for whole liver. During the latter period the amount of insulin had to be doubled to control the diabetic state. In this case, judging from the clinical progress of the patient, the liver extract did not lower the blood sugar concentration, on the contrary, the amount of insulin had to be doubled to control the diabetes.

In connection with the question of the effect of liver extract on the carbohydrate metabolism, Gensslen's¹⁰ report seems to throw some light on the probable mode of action of some liver extracts. He gave normal rabbits injections of a potent liver extract and found that after injection of 0.5 cc of the extract daily for several days the animal's hepatic glycogen, which normally ranges between 4 and 6 per cent, practically disappeared. From this experiment it would appear that this liver extract had a glycogenolytic effect on the hepatic glycogen.

Buttner¹¹ conducted similar experiments with a protein-free liver extract. Seven out of 9 patients who were given injections of 2 cc of this extract showed increases in the blood sugar averaging 33 per cent, the maximum increase running as high as 60 per cent. Similar results were obtained by the same author in experiments with normal rabbits. To exclude the influence of the adrenal glands he repeated these experiments with adrenalectomized and morphine-

poisoned animals. The results, however, remained the same.

My own experience with the effect of liver extracts on the carbohydrate metabolism goes back to the years 1932 and 1933. During this period 17 patients, all suffering from pernicious anemia, were treated by me with liver extract¹² for various lengths of time. The routine treatment consisted of intramuscular injections of liver extract given twice weekly. The extract was intended for parenteral administration and was delivered in individual ampules containing about 5 cc of the extract. I used two fractions of the extract, they were labeled extract fraction A and extract fraction B. To test the potency of these fractions the patients were divided into two groups. One group received regularly the fraction A extract, while the other group was treated with the fraction B extract. The hematologic response to both extracts was good.

REPORT OF CASES

CASE 1—A woman in her late fifties who was treated with the fraction B extract soon began to complain of a severe itching in the vulva. A determination of the fasting blood sugar and an examination of the urine were therefore made. The urine gave a positive reaction for sugar with Benedict's reagent, and the blood sugar was reported to be at 150 mg per hundred cubic centimeters. A month later another determination of the blood sugar was made. This time the value rose to 190 mg. The patient was then referred to the clinic for diabetic patients and the antianemia treatment with the extract was continued. Six weeks later the blood sugar was found to have reached a concentration of 240 mg per hundred cubic centimeters. Since the coexistence of diabetes and pernicious anemia was always regarded as extremely rare, this case aroused my interest. In investigating the case it was important to establish whether the diabetes preceded the anemia or developed after it. This could easily be established since the patient had been referred to the clinic from the ward. The hospital record showed that about six months previously the blood sugar was 90 mg per hundred cubic centimeters and the urine was normal.

The assumption that the liver extract might in some way be connected with the development of the diabetes, especially after consideration of the steady and rapid rise in the blood sugar concentration could not easily be dismissed. To make sure that this was not a mere coincidence, I examined the urine and the blood of several other patients who had been treated with the same extract. The results of these examinations confirmed my suspicions. All had hyperglycemia and glycosuria.

CASE 2—M. C., a man about 60 years old, had suffered from pernicious anemia for some years. On a recent admission to the hospital his blood sugar was found to be 110 mg per hundred cubic centimeters and his urine was free of sugar. After four weeks of treatment with the fraction B extract his blood sugar was 140 mg per hundred cubic centimeters and his urine gave a positive reaction for sugar with Benedict's

8 Brett, P., Broom, W. A., and Howitt, F. O. *Lancet* **1** 20, 1931.

9 Bowen, B. D. Comparative Effect of Liver and Liver Extract on Diabetes in Case of Combined Pernicious Anemia and Diabetes, *J. A. M. A.* **95** 30 (July 5) 1930.

10 Gensslen, M. *Klin. Wchnschr.* **9** 2099, 1930.

11 Buttner, H. E. *Klin. Wchnschr.* **11** 1218, 1932.

12 The extract was supplied by the Wilson Laboratories, Chicago. 1 Gm of the extract represents 25 Gm of fresh liver.

reagent Four weeks later the blood contained 190 mg of dextrose per hundred cubic centimeters Six weeks later, with the patient still under treatment with fraction B extract, the blood sugar reached a level of 240 mg Several weeks later it rose to 320 mg

CASE 3—Another patient in this group, E S, a man, whose blood sugar had been found to be normal about a year previously, had values ranging between 190 and 300 mg per hundred cubic centimeters of blood after several months of treatment with the fraction B extract

COMMENT

The remaining 5 patients of this group reacted in the same way to the administration of

Fasting Blood Sugar Values and Urinary Reactions of Seventeen Patients with Pernicious Anemia Treated with An Injectable Liver Extract, Fraction A or B

No	Name	Sex	Fasting Blood Sugar Mg per 100 Cc of Blood		Urine
			Before Liver Treat- ment	During Liver Treat- ment	
1	M O	M	110	140-320	Glycosuria
2	E S	M		180-300	Glycosuria
3	N A	F	90	150-240	Glycosuria
4	R S	F	?	190	Glycosuria
5	O R	F	90	190	Glycosuria
6	M R	F	?	140-160	Glycosuria
7	R K	F	?	140-160	Glycosuria
8	N G	M		140-160	Glycosuria
9	A N	M	120	150	No sugar
10	S W	M	100	150	No sugar
11	P C	F	95	140	No sugar
12	H H	F	100	90	No sugar
13	H D	M	120	140	No sugar
14	M T	F	100	105	No sugar
15	M D	M		90	No sugar
16	H G	M		105	No sugar
17	O S	F		120	No sugar

the extract All had dextrose in the urine and hyperglycemia in some degree In several instances I was able to determine the blood sugar concentration just before the treatment with this extract was started I found that after six to eight injections of liver extract fraction B all patients had a 40 to 50 per cent rise in the blood sugar concentration, and 1 patient had glycosuria

Further observation of these patients could not be made by me because of my resignation from the clinic However, the attending physician, who is still in charge of the clinic, was kind enough to give me some later information about these patients In a letter addressed to

me in 1942 he wrote "Some of the cases you worked on have been established definitely now as instances of diabetes, and the hyperglycemia may not necessarily have developed as a result of the liver extract"

Personally, I have no doubt that the liver extract was responsible for the development of the diabetes There is enough clinical and laboratory evidence today to support this statement

The experiments conducted by Dr Joseph E Sokal in Dr Long's laboratories proved conclusively the presence of a glycogenolytic substance in the liver extract I used in the clinic for the treatment of patients with pernicious anemia This extract when injected into normal rabbits regularly produced glycosuria and hyperglycemia

SUMMARY

A liver extract¹² used in the treatment of patients with pernicious anemia was found to have an effect on the carbohydrate metabolism Of the 17 patients treated with this liver extract, fraction A or B, 11 had an increase in the blood sugar concentration, 8 had glycosuria and hyperglycemia in various degrees, depending on the length of treatment, and the remaining 6 were unaffected Some of the patients became permanently diabetic

CONCLUSIONS

1 Judging from clinical observations and experimental work in the laboratory, it appears that some liver extracts used in the treatment of pernicious anemia contain an as yet unknown factor, not identical with the antianemia principle, which is capable of producing glycosuria and hyperglycemia in human beings as well as in experimental animals

2 All liver extracts before being released for public use should be tested for the presence of this "diabetogenic" factor

3 Extracts possessing such properties could be used effectively in the treatment of chronic hypoglycemia

4 Periodic determinations of blood sugar should be made for all patients treated with liver extract

EFFECTS OF SOME LIVER EXTRACTS ON CARBOHYDRATE METABOLISM

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INTRODUCTION AND REVIEW OF THE LITERATURE

The announcement by Minot and Murphy of the successful therapy of pernicious anemia by a liver diet served as a strong stimulus to the preparation and study of liver extracts. Although the primary interest of investigators has been in the effect of various liver extracts on the hemopoietic system and most of the studies have been confined to patients with pernicious anemia, there has been some consideration of the action of such extracts on other organ systems. With the introduction of injectable extracts in particular, animal experiments have been performed and various side actions of liver preparations have been studied.

In the course of such studies of the systemic effects of orally and parenterally administered liver extracts, especially the latter, various observers have noted more or less striking effects on the carbohydrate equilibrium of the body. As might be expected with different men using various techniques and working with extracts prepared often by widely divergent methods, there is no agreement in the reported results. Thus one finds papers denying any effect of liver extract on carbohydrate metabolism, opposed by reports of clearcut and definitely established actions, in opposing directions.

Because of the contradictory nature of the findings and because much of the investigation has been poorly controlled, accurate appraisal and evaluation of the published work are difficult. The reports in the literature fall into several groups.

Effect of Liver Extract on Blood Sugar in Experimental Animals—Buttner¹ found that both of two commercial extracts tested produced

regularly a more or less distinct rise in the blood sugar of fasting and fed rabbits. In the latter, after feeding of levulose increases of more than 150 mg per hundred cubic centimeters above the values for the control animals were noted. The blood sugar-raising effect was noted in adrenalectomized and in morphine-poisoned rabbits. Kahler and Riedel² were unable to confirm Buttner's results. However, the latter³ raised certain valid objections against the experimental technic and dosage that they used. Zipf and Dringenberg⁴ also were unable to confirm Buttner's findings. They examined four liver preparations, including the two used by Buttner, and obtained no consistent effect on the fasting blood sugar, alimentary hyperglycemia or insulin hypoglycemia of rabbits. On the other hand, Hungerland⁵ noted that daily injections of liver extract into rabbits for four to seven weeks produced a resistance to insulin and a rapid recovery from insulin hypoglycemia as compared with the course in controls.

Effect of Liver Extract on Glycogen Content of Liver—Gaensslen⁶ noted that injection of his liver extract into guinea pigs caused a prompt and remarkable drop in hepatic glycogen. He obtained values ranging from a trace to 15 per cent, as against 48 per cent and 5 per cent in control animals. Ederle and Kriech⁷ also noted a glycogenolytic effect of liver extract and ascribed it to the protein content of the extracts used. De Caro⁸ reported that administration of

2 Kahler, H., and Riedel, R. Does Liver Extract Exert an Effect on Blood Sugar? *Klin Wchnschr* **12** 151, 1933.

3 Buttner, H. E. Liver Extracts. Effect on Blood Sugar. *Klin Wchnschr* **12** 152, 1933.

4 Zipf, K., and Dringenberg, H. The Effect of Liver Extract on Carbohydrate Metabolism, *Arch f exper Path u Pharmacol* **170** 465, 1933.

5 Hungerland, H. The Effect of Liver Extract on Insulin Hypoglycemia. *Klin Wchnschr* **18** 647, 1939.

6 Gaensslen, M. A Highly Active Injectable Liver Extract. *Klin Wchnschr* **9** 2099, 1930.

7 Ederle, W., and Kriech, H. Hepatic Glycogenolytic Action of Organ Extracts Containing Protein, *Med Welt* **6** 184, 1932.

8 De Caro, L. The Action of Liver Extract on Hepatic Glycogen and Basal Metabolism, *Boll Soc s' i di biol sper* **7** 344, 1932.

From the Department of Physiological Chemistry, Yale University Medical School.

Dr C. N. H. Long and Miss Edith Fry gave advice and criticism during the studies reported and made laboratory facilities available.

1 Buttner, H. E. Clinical and Experimental Observations on the Action of Injectable Liver Extracts, *Klin Wchnschr* **11** 1218, 1932.

liver extract caused a decrease in hepatic glycogen in the rat and guinea pig, without affecting blood sugar or basal metabolism. On the other hand, Wiedemann⁹ found that liver extract caused a rise in hepatic glycogen. He obtained values as high as 11.3 per cent in normal guinea pigs.

Effect of Liver Extract on Blood Sugar of Human Subjects—The reports by Blotner and Murphy¹⁰ that oral administration of liver extract had a favorable effect on the blood sugar of diabetic patients aroused much interest. However, later careful work with clinical material and depancreatized dogs (De Pencier, Soskin and Best¹¹) failed to confirm these startling findings. There are several instances on record in which hyperglycemia and glycosuria have been observed in the course of treatment of patients with pernicious anemia with crude liver extract. The most striking of these is the experience of H. B. Sokal,¹² who found that hyperglycemia developed in 11 of 17 patients treated with a crude liver extract and that 8 of them had glycosuria.

The striking values for liver glycogen obtained by Gaensslen and those for blood sugar obtained by H. B. Sokal after parenteral administration of liver extract prompted this study of the effect of liver extract on certain aspects of carbohydrate metabolism. Aims of the work reported herein were (a) to confirm if possible the results described by these investigators, (b) to study the mechanism involved and (c) to investigate the properties of the fraction responsible (it seemed most probable that the carbohydrate-affecting fraction was independent of the anti-anemic factor).

Several liver extracts were available for study, among them three similar to those used by H. B. Sokal. Unfortunately, extracts used by other authors cited could not be obtained. It was most feasible to use the albino rat as the experimental animal.

9 Wiedemann, A. Effect of Liver Extract on the Carbohydrate Metabolism of the Liver, *Klin Wchnschr* **17** 766, 1938.

10 Blotner, H., and Murphy, W. P. Effect of Certain Liver Extracts on the Blood Sugar of Diabetic Patients, *J. A. M. A.* **94** 1811 (June 7) 1930.

11 De Pencier, M. T., Soskin, S., and Best, C. H. The Effect of Liver on the Blood Sugar Level and on the Sugar Excretion of Depancreatized Dogs, *Am. J. Physiol.* **94** 548, 1934.

12 Sokal, H. B. Does Liver Extract Contain a Diabetogenic Substance? Report of Eight Cases of Pernicious Anemia with Hyperglycemia and Glycosuria, unpublished data, personal communication to the author (1934).

PLAN OF EXPERIMENTS

Preliminary experiments included brief examination of the liver extracts available, selection of a standard dilution of the concentrate in which the bulk of the extract used was supplied, selection of experimental animals and standardization of technic. Investigation then proceeded along the following lines:

I Daily determination of urinary dextrose over long intervals, both during administration of liver extract and during control periods.

- A In normal animals
- B In "latent" diabetic (partially depancreatized) animals
- C In a "frankly" diabetic (partially depancreatized) animal excreting large amounts of dextrose daily

II Effect of parenteral liver extract on blood dextrose levels of normal animals

- A In the fasting state
- B In the absorptive and postabsorptive states

III Effect of insulin on hyperglycemia produced by liver extract

IV Effect of liver extract on carbohydrate stores of normal animals

- A Fasting
- B Fed

V Effect of parenteral liver extract on nitrogen balance of normal animals

VI Effect of parenteral liver extract on respiratory quotients of

- A Normal animals
 - 1 Fasting
 - 2 During absorption of dextrose
- B "Diabetic" (partially depancreatized) animals
 - 1 Fasting
 - 2 During absorption of dextrose

Finally, some properties of the active principle were studied, and attempts were made to fractionate the liver extract used. Postmortem studies and microscopic examination of representative tissue sections were carried out routinely, all animals being killed at the conclusion of the experiments.

METHODS

Care of Animals—The animals were housed in a warm room, free from drafts. They were weighed, food cups and water bottles were filled and urine flasks were emptied at the same time each morning. Cages were cleaned at regular intervals. Rats were main-

tained in cages consisting of large galvanized iron cans equipped with no. 4 mesh wire screening as a bottom and with a removable top. These cages rested on 10 inch (25 cm) glass funnels.

Diet—Rats were given a standard diet, prepared in bulk, which contained 25 per cent free carbohydrate and 52 per cent total available carbohydrate.

Collection and Analysis of Urine—Urine was collected in 125 cc Erlenmeyer flasks containing about 1 cc of toluene. No preservative was used when it was desired to apply fermentation tests to the urine.

Urinary dextrose was determined by titrating undiluted urine against 5 cc of Benedict's quantitative solution. Urinary nitrogen was determined by a modification of the Folin-Wu¹³ method, with the comparative colorimeter.

Collection and Analysis of Blood—Blood was obtained for determination of dextrose by rapidly cutting off the tip of the animal's tail with a sharp razor blade. This procedure was usually painless, and blood was readily obtained with the aid of gentle massage of the cut tail. About 0.2 cc of blood was collected for analysis, a small amount of potassium oxalate-sodium fluoride mixture serving as anticoagulant and preservative.

Dextrose was determined by a modification of the Folin ferricyanide reduction micromethod. The Evelyn photoelectric colorimeter was used, readings were converted into logarithmic equivalents and values for blood dextrose were read directly off a previously prepared and frequently checked curve.

Determination of Glycogen—Tissues for determination of glycogen were obtained from the living animal anesthetized with pentobarbital sodium (5 mg per hundred grams of body weight). As soon as anesthesia was complete the skin of the leg was incised and reflected back, so that the gastrocnemius muscle was exposed. The muscle was rapidly freed along its length and cut at the achilles tendon and proximally, a sample of about 1 Gm being taken. This sample was immediately plunged into a 50 cc tared centrifuge tube containing 2 cc of 30 per cent potassium hydroxide solution. An abdominal incision was then made, a lobe of the liver clamped off and approximately 1 Gm of hepatic tissue removed. This was quickly blotted on filter paper to remove excess blood and similarly dropped into a tared tube containing 30 per cent potassium hydroxide solution. Finally, 1 cc of blood was drawn by cardiac puncture, for a check determination of dextrose.

Glycogen was precipitated with alcohol, hydrolyzed with hydrochloric acid and determined as dextrose by the Shaffer-Somogyi method. The blood filtrate was prepared by the Somogyi zinc precipitation method and similarly analyzed for dextrose.

Determination of Respiratory Quotients—The open circuit Haldane apparatus was used for determining respiratory metabolism. The rat was placed in a Mason quart jar fitted with a large rubber stopper carrying an inlet and an outlet tube. Incoming air was purified by passing it successively through sulfuric acid and pumice, soda lime and anhydrous magnesium perchlorate^{14a}. Thus it was freed of water and carbon dioxide. Emerging air was passed through two U tubes containing anhydrous magnesium perchlorate and two containing sodium hydroxide-asbestos absorbent^{14b} and

anhydrous magnesium perchlorate in that order. In this manner expired water and carbon dioxide were absorbed. The final tube was attached to a mercury manometer and a vacuum line, which drew the air through the system. The entire system (excluding the tubes used in purification of incoming air) was weighed before and after each trial. Carbon dioxide was determined directly, by the change in weight of the tubes containing sodium hydroxide-asbestos absorbent. The gain in weight of the system as a whole (rat + jar + U tubes) represented the oxygen consumed.

Liver Extracts—Extracts "fraction A" and "fraction B" (the fractions used by H. B. Sokal in the treatment of patients with pernicious anemia) were specially prepared by the Wilson Laboratories, Chicago. The extract used most frequently in these experiments, which will be designated liver extract no. 1, was prepared frequently in small quantities by diluting with an equal volume of distilled water another extract specially prepared by the Wilson Laboratories. The diluted extract

TABLE 1—Fermentation of Liver Extracts

Extract	Dilution	Dextrose Equivalent	Yeast	Results
Fraction B		13.0%	Bakers'	Partial fermentation
L E 1	1:5	2.7%	Bakers'	No fermentation
L E 1	1:5	2.7%	Same sample	No fermentation
Dextrose	3%	3%	bakers'	No fermentation
Dextrose	0.8%	0.8%		Slow fermentation
L E 1	1:5	2.7%	Brewers'	Slight fermentation
Lilly	1:10	0.6%	Brewers' and bakers'	Complete fermentation
L E 1	1:9	1.5%	Same sample	Slight fermentation
L E 1 plus 0.1 Gm dextrose	1:9	2.0%	mixed brewers' and bakers'	Fermentation equivalent to added dextrose
Dextrose	0.5%	0.5%		Complete fermentation
L E 37	1:10	1.0%		No fermentation
L E 37 plus dextrose	1:10	1.5%	Same sample bakers'	Partial fermentation
L E 33	1:10	1.0%		No fermentation
L F 33 plus dextrose	1:10	1.5%	Same sample bakers'	Partial fermentation

was a clear, deep brown, neutral solution, of specific gravity 1.14. Fifteen grams of fresh liver was represented by 1 Gm of this extract, it contained 30 per cent of solid material and 2.6 per cent of ash. Its reducing power was equivalent to a 13.5 per cent solution of dextrose and it contained 22 mg of nitrogen per cubic centimeter. It was almost completely dialyzable. Other extracts only briefly used, were Wilson's (1938) Lilly's (1939) plain and Abbott's (1940) concentrated liver extracts.

These six commercial liver preparations at one time or another found to be efficacious in the treatment of pernicious anemia, were examined in this study. All were soluble in water, completely or with only small amounts of insoluble residue, forming a neutral deep colored solution. All were free of protein as judged by the heat precipitation, biuret, Millon and nitric acid tests. None contained a significant amount of other soluble material, all contained nitrogen.

A disturbing factor throughout the experiment has been the fact that four of the extracts tested included all those capable of producing glycosuria in rats.

13 Folin, O., and Wu, H. A System of Blood Analysis, J Biol Chem 38:81, 1919.

14 (a) The preparation of anhydrous magnesium perchlorate used was "dehydrite." (b) The preparation of sodium hydroxide and asbestos was "ascarite."

gave strong reductions with Benedict's solution, equivalent to a dextrose concentration of 6 to 14 per cent. The extracts which reduced Benedict's solution behaved like equivalent solutions of dextrose toward the common sugar reagents. It was therefore attempted to identify the reducing material as dextrose. To this end, condensation with phenylhydrazine and fermentation tests were used. Various dilutions of three of the potent preparations were condensed with phenylhydrazine in the usual manner, dextrose solutions of equivalent reducing power being used as controls. In all cases crystalline precipitates were readily obtained which grossly resembled glucosazone and microscopically could not be distinguished from it. Fermentation tests with the liver extracts were rather unsatisfactory. Difficulty was experienced in obtaining potent samples of yeast and in achieving consistent results in attempts at fermentation of the extract. A complicating factor making the interpretation even more difficult was the presence of various preservatives in the extracts tested. The results of fermentation tests are listed in table 1. It will be seen that, although partial fermentation was obtained occasionally and complete fermentation was secured in 1 instance, the results on the whole cannot be regarded as satisfactory.

EXPERIMENTAL STUDIES

Production of Glycosuria by Parenteral Administration of Liver Extract and Assay of Several Preparations—It was found possible to produce glycosuria consistently by subcutaneous or intraperitoneal injection of several liver extracts. In normal animals urinary excretion of dextrose of as much as 0.4 to 0.8 Gm. per day was obtained with large doses of extract. That the reduction noted was in reality due to dextrose was readily proved. Glucosazone was obtained by condensing samples of urine with phenylhydrazine, reduction of Benedict's solution was absent after fermentation of the urine with yeast.

The six liver extracts already mentioned were tested for ability to produce glycosuria. Three of these preparations are now in use in the treatment of pernicious anemia. The others, relatively cruder, were formerly found to be effective against that disease but have been replaced by more potent and pure preparations, these three, designated as "fraction A," "fraction B" and "liver extract no. 1," are samples prepared to resemble the extracts used by H. B. Sokal¹² in the work previously cited. The relative potency of these extracts was tested by administering various amounts of each parenterally to normal animals, under well controlled conditions. In some cases it was immediately apparent that an extract either had little ability to produce glycosuria or was potent enough to warrant further study, in other cases an extended period of observation was necessary to reach a conclusion.

Chart 1 presents a typical study of this sort. In this experiment, "fraction A" and "fraction B"

were compared, three normal male guinea pigs weighing 250 to 300 Gm., on a diet of oats and lettuce, were used. Guinea pig S 1 was given an injection of "fraction B", animal S 2 received an equal dose of "fraction A" under the same conditions, S 3, a control, was occasionally given an injection of dextrose solution. It will be noted that the control animal at one time excreted a significant amount of dextrose and that the experimental animals did not do so unless they were given liver extract. Administration of 0.2 cc. of the extract per hundred grams of body weight did not produce a glycosuric response. Administration of 0.4 cc. per hundred grams of either fraction A or fraction B evoked glyco-

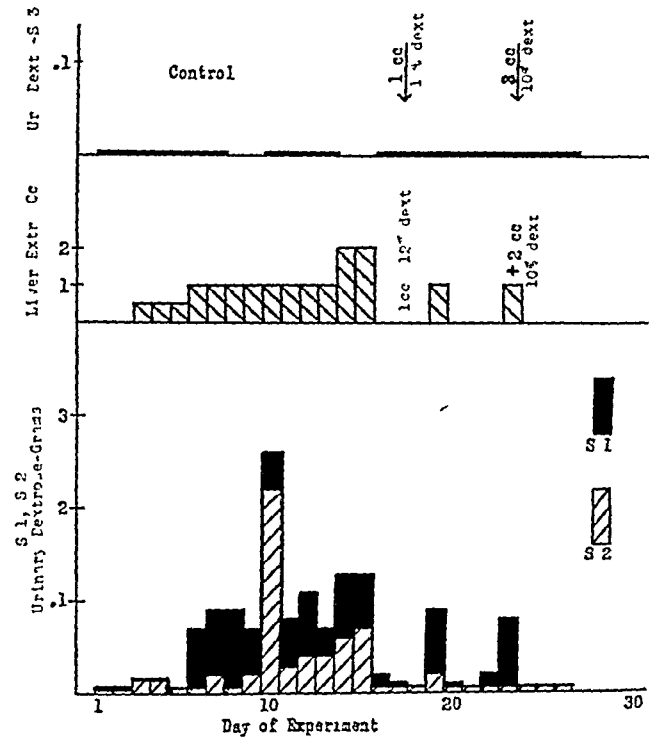


Chart 1—Activity of two liver extracts on 3 normal male guinea pigs weighing 250 to 300 Gm., on a diet of oats and lettuce. S 1 was given fraction B, S 2 received fraction A, S 3 was the control.

suria, the response to fraction B was in every case greater than that to fraction A. Furthermore, after twenty-three days fraction A was no longer capable of eliciting glycosuria, whereas fraction B was as active as before. Doubling the dose of liver extract, to 0.8 cc. per hundred grams of body weight, resulted in a 69 per cent increase in urinary dextrose. Injections of dextrose solutions, alone or in conjunction with liver extract, had no effect on glycosuria. The possibility that individual variation played a role was ruled out by later giving animal S 2 an injection of fraction B, when a glycosuric response was again obtained in this animal.

Table 2 summarizes the results of comparative studies of potency of the various extracts.

The extracts were tested in some cases in the same animal at different times, in other cases in 2 animals of the same sex, age and weight, maintained under identical conditions. If the latter type of test was used, individual variation was ruled out by changing extracts at the conclusion of the experimental period, as first de-

TABLE 2—Activity of Several Liver Extracts

Extract	Description	Reduction Dextrose Equivalent	Experimental Animal	Glyco- suria Produced
Wilson	Now manu- factured for treatment of pernicious anemia	0	Normal guinea pig	1 plus
Fraction A	No longer used	10%	Normal guinea pig, normal mouse	2 plus
Fraction B	No longer used	12%	Normal guinea pig, normal mouse, normal and diabetic rat	4 plus
L E 1	No longer used	13.5%	Normal and diabetic rat	4 plus
Lilly	Now used in the treatment of pernicious anemia	6.0%	Normal rat	2 plus
Abbott	A "concen- trated" liver extract, relatively pure, now used in the treatment of pernicious anemia	1.3%	Normal rat	0

scribed. It will be seen that the most active preparations were fraction B and liver extract no 1.

Selection of Experimental Animals and Standardization of Procedure—Guinea pigs, mice and rats were given injections of potent liver extract, and glycosuria was obtained in each species. Mice proved to be unsuitable, however, because only small amounts of urine were obtained and samples were usually grossly contaminated with feces. Both guinea pigs and rats were satisfactory, but the latter proved much more convenient as experimental animals because it was possible to house them in the departmental rat colony and feed them a standard diet of known composition. Accordingly, normal and depancreatized rats were the animals used in the subsequent experiments. The care and feeding of these animals and the collection of urine have already been described under "Methods."

It has been pointed out that fraction B and liver extract no 1 were the two extracts found to be highly potent. These were very similar, and since liver extract no 1 was somewhat the more active of the two and a larger quantity of it was available, it was decided to use that

preparation in the remainder of the experiments. In the work to be reported in the rest of this paper, therefore, liver extract no 1 is the extract used unless specific mention is made to the contrary.

Both subcutaneous and intraperitoneal injections were used. The former frequently caused a superficial ulcer at the site of an injection; furthermore, it was sometimes possible for a significant portion of the dose administered to be extruded after its injection. Intraperitoneal injections were more satisfactory on the whole; they had the disadvantage, however, of occasionally resulting in a fatal accident. Injections were usually made between 10 and 11 o'clock in the morning under the same conditions from day to day.

Studies on Glycosuria Produced by Liver Extract—Daily determinations of urinary dextrose were made on three types of experimental animals under the influence of active preparations of liver extract. The effects of various levels of dosage and of food intake were studied.

Chart 2 shows the dextrose excretion of a normal rat having free access to food and water over a period of forty days. Several dose levels of "fraction B" were used and on several occasions the animal was given an injection of dextrose solution. The graph illustrates a somewhat more uniform response than was usually obtained but is otherwise typical. It is seen that the animal excreted significant amounts of dextrose only when given injections of liver

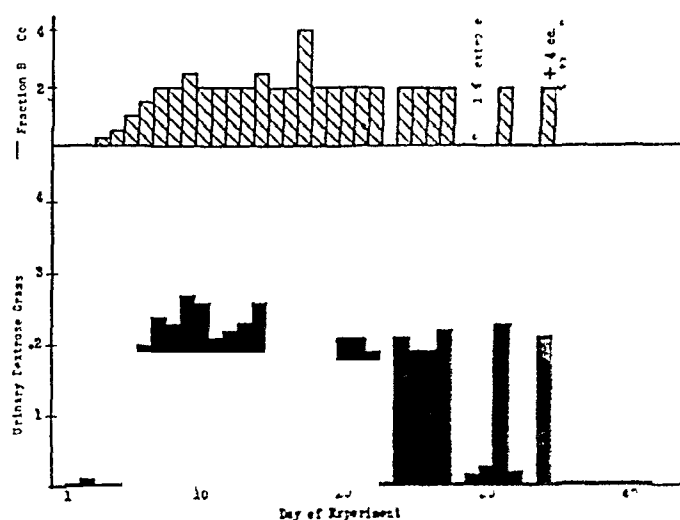


Chart 2—Excretion of dextrose by a normal rat weighing 400 Gm, on a standard diet, given injections of an active liver extract.

extract and that the amount excreted was proportional to the dose of the extract administered. The threshold dose was found to be 0.25 cc per hundred grams of body weight. 130 mg of dextrose was excreted at that level. With a

dose of 0.5 cc per hundred grams, the urinary excretion rose to about 210 mg, and on one occasion, when 1 cc per hundred grams was administered, 420 mg of dextrose appeared in the urine. Injection of dextrose solution, alone or with liver extract, had no effect on urinary dextrose.

In other experiments with normal animals it was found that the excretion of dextrose occurred in the first six hours after administration of liver extract. Glycosuria was diminished but not abolished when liver extract was administered in the fasting state. Injection of liver extract in conjunction with feeding of dextrose solution by stomach tube caused a twofold to threefold increase in urinary dextrose; this interesting experiment will be discussed later. Feeding of dextrose alone caused no glycosuria.

Two rats with "latent diabetes" were available. These were partially depancreatized animals that manifested no glycosuria normally, but were susceptible to the "diabetogenic" hormone of the anterior lobe of the pituitary gland. These animals behaved in general like normal rats toward one or two doses of liver extract, although they were somewhat more sensitive to its action, excreting 30 to 50 per cent more dextrose than normal rats receiving the same dose. It was noted, however, that administra-

tion of liver extract over a period of days caused a general increase in the glycosuria produced by a given dose, and in one animal a "diabetic" state was produced which persisted for two days after the last injection. These findings are reported in table 3.

TABLE 3—Effect of Liver Extract and Anterior Pituitary Extract on Two Partially Depancreatized Rats

Animal	Injection	Urinary Dextrose, Mg
S 4	Foreperiod	0
	Saline anterior pituitary extract	
	0.5 cc /100 Gm, on 2 successive days	2d day 250
	L E 1	
	0.5 cc /100 Gm, 1 dose	Average 150
Y 125	0.5 cc /100 Gm, 5 daily doses	Average, 5th day 180
	Foreperiod	0
	Saline anterior pituitary extract	
	0.5 cc /100 Gm, 1 dose	
	0.5 cc /100 Gm, 2 daily doses	2d day 210
	L E 1	
	0.5 cc /100 Gm, 1 dose	Average 160
	0.5 cc /100 Gm, 5 daily doses	Average, 5th day 230
	0.5 cc /100 Gm, 9 daily doses	9th day 690
	No injection	10th day 220
	No injection	11th day 100

tion of liver extract over a period of days caused a general increase in the glycosuria produced by a given dose, and in one animal a "diabetic" state was produced which persisted for two days after the last injection. These findings are reported in table 3.

Finally, the effect of liver extract on the dextrose excretion of a spontaneously diabetic animal was studied. Y-125, a depancreatized rat

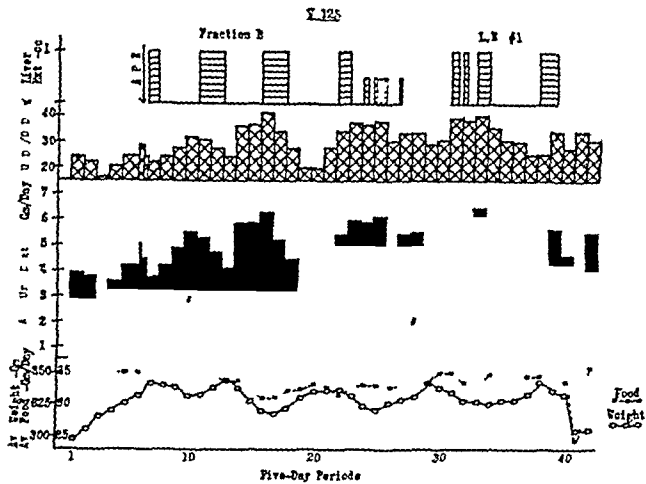


Chart 3—Data on a diabetic rat given injections of active liver extracts. Weight, food intake, total dextrose excreted and dextrose excretion as percentage of available dietary dextrose were charted for 210 days in five day averages. $UD/DD\% = \frac{\text{Dextrose in urine} \times 100}{\text{Carbohydrate in diet } 60\% \text{ of protein } 10\% \text{ of fat}}$ A P E indicates a single injection of saline extract of anterior pituitary, 0.5 cc per hundred grams of body weight.

dextrose were attained during or shortly after administration of liver extract. The ratio of urinary dextrose to total available dietary dextrose (available dietary dextrose = carbohydrate plus 60 per cent of protein plus 10 per cent of fat), a better index of severity of the diabetic state, shows an even closer relation than the other factors to injections of liver extract. It is seen, however, that there is no correlation between the output of dextrose and the dose of liver extract; in fact, the greatest concentration of the diabetic state of this animal occurred at a time when it was receiving small doses of extract every other day.

The intensity of the effect produced in this animal is best gaged by examining its previous record. During the month preceding the start of this experiment, its average daily output of dextrose was 4.02 Gm. Injection of a saline extract of the anterior lobe of the pituitary increased the excretion of dextrose from 4.3 to 5.1 Gm. The highest single day's output at any time previous to the injections of liver extract

was 5.8 Gm. In the course of the experiment, however, an output of 7.5 Gm was attained on three occasions. It is not fair, of course, to compare the effect produced by continued administration of liver extract with that obtained by only one dose of anterior pituitary extract, it is obvious, however, that this animal's diabetic state was at least as readily accentuated by liver as by pituitary extract.

Effect of Liver Extract on Blood Sugar of Normal Animals—It was found that intraperitoneal injection of liver extract caused a remarkable rise in blood sugar in fasting animals. Figure 4 contains two of the blood sugar curves

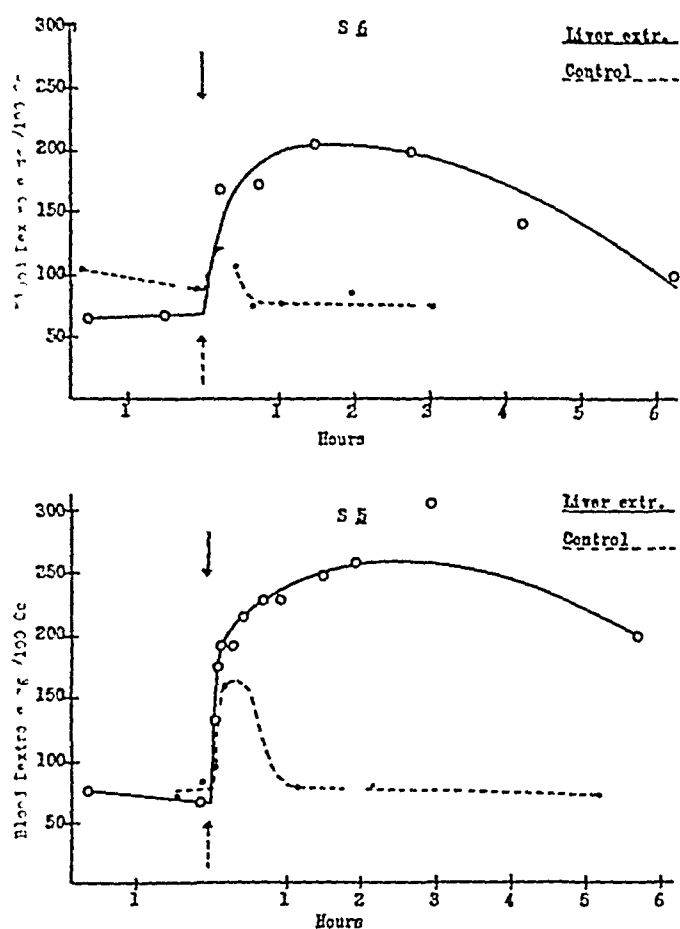


Chart 4—Response of normal fasting rats to injections of liver extract. The control received 1.5 cc of 14 per cent dextrose solution.

and is typical of the results obtained. S 5 and S 6 were normal female rats which were made to fast for thirty hours and were given injections of 0.67 cc of liver extract no. 1 per hundred grams of body weight. Control curves represent the same rats given injections of 14 per cent dextrose solution under similar conditions. Table 4 presents the data obtained in the experiments on fasting normal rats given injections of liver extract. The blood sugar curves in chart 4 were compared with curves obtained after injection of 14 per cent dextrose solution. This procedure is valid only if the reducing power of the liver extract is due to dextrose, or

to something readily metabolized to dextrose in the body. It is conceivable that the extract may contain a nondextrose reducing substance which is not rapidly disposed of by the organism and which would therefore persistently give false high values for blood sugar; this possibility was not rigorously excluded by the analysis of the extract.

TABLE 4—Effect of Liver Extract on Fasting Blood Sugar of Normal Rats*

Time	Blood Sugar Values, Mg per 100 Cc	Average	No of Observations
21-36 hour fasting	87, 70, 58, 75, 67, 105, 90, 85, 79, 67, 81, 62, 64, 40, 40	72	15
½ hour after injection of L. E. 1	200, 170, 156, 218, 167, 170, 130, 115	166	8
1 hour after injection	173, 184, 230, 200	197	4
2 hours after injection	182, 205, 258, 200	211	4
4 hours after injection	240, 140	190	2

* Intraperitoneal injection, usually 0.67 cc of liver extract no. 1 per hundred grams of body weight.

Accordingly the following experiment was performed.

A fasting animal was given an injection of liver extract. One hour later a lethal dose of insulin was administered and blood sugar values were obtained at intervals until the animal's death. If the high figures recorded in table 4 were due to a nondextrose reducing substance which persists in the rat's blood stream for several hours, the animal should have a relatively high blood "sugar" even though in insulin shock. If, on the other hand, these figures actually represented dextrose, the blood sugar reading should be extremely low at death. This experiment is recorded in table 5. It is seen that

TABLE 5—Effect of Insulin on the Rise in Fasting Blood Sugar Caused by Liver Extract

Time, Hours	Injection	Comment	Blood Sugar, Mg per 100 Cc
0		Fasted 12 hours	40
0	0.67 cc L. E. 1/100 Gm		
1	7 units insulin/100 Gm		131
1½			76
2		Animal drowsy	51
2½		Mild ataxia	41
3		Tremors	10
4	1 Gm dextrose	Comatose	0
5		Roused slightly, died	10

rat S 5 succumbed with a blood sugar of 0, effectively excluding the presence of any reducing substance in the blood stream. Therefore, even if there is a noncarbohydrate reducing substance in the liver extract, it is not found in the blood of the experimental animal several hours after the injection.

In the course of some of the experiments to be reported an opportunity was afforded to examine the effect of intraperitoneal injection of liver extract on normal rats in the absorptive state. As might be expected, the blood sugar curves were similar to those obtained for fasting animals, but the levels of dextrose were considerably higher, reaching 425 and 350 mg per hundred cubic centimeters in the two curves obtained. These figures are shown in table 6.

TABLE 6—Effect of Liver Extract on the Carbohydrate Stores of Normal Rats *

Animal		Liver Glyco gen, %	Muscle Glyco gen, %	Blood Sugar, Mg per 100 Cc
S 9	Control, injection of dextrose every 4 hours for 24 hours	1.34	0.59	115
S 8	Injection of dextrose every 4 hours for 12 hours, then L. E. 1 every 4 hours for 12 hours	0.5	0.6	146
S 10	Same as S 8	0.52	0.36	70
S 11	Control, dextrose feeding plus injection of dextrose every 4 hours for 24 hours	6.0	1.34	130
S 12	Dextrose feeding plus injection of dextrose every 4 hours for 12 hours, then dextrose feeding plus L. E. 1 every 4 hours	Died 17th hour		
S 13		Died 17th hour		
S 14		0.33 Died 20th hour		14th hr 320 16th hr 360 20th hr 425
S 16	Dextrose feeding, L. E. 1 at 4 hours, killed at 7 hours	2.06	0.54	230 ?
	Control (Cori Cori ¹⁵)	(5.0)	(0.55)	(113)
S 17	L. E. 1, dextrose feeding at ½ hour, killed at 4½ hours	1.93	0.42	0.40 ½ hr 113 1 hr 139 2 hr 270 3½ hr 350 4½ hr 350
	Control (Katzin ⁹)	(4.0)	(0.78)	(114)
	Control (Ferguson ²⁰)	(3.1)	(0.68)	(147)

* All the animals were made to fast for twenty-four hours before the beginning of the experiment. Liver extract 1 and 14 per cent dextrose solution were given in doses of 0.67 cc per hundred grams of body weight, the dextrose feeding was 720 mg per hundred grams.

Effect of Liver Extract on Carbohydrate Stores of Normal Rats—The effect of repeated injections of liver extract on muscle and liver glycogen of fasting rats was studied as follows.

Three rats were made to fast for twenty-four hours. They were then placed in metabolism cages, and urine was collected for twelve hours, during which time each rat received three injections of 0.67 cc of 14 per cent dextrose solution per hundred grams of body weight. (This was done to obtain control values for studies of nitrogen balance, to be reported.) In the course of the next twelve hours, when second specimens of urine were being obtained, 2 animals received 3 injections of 0.67 cc of liver extract no. 1 per hundred grams of body weight, while the third, a control, continued to receive the dextrose solu-

tion. At the end of the second twelve hours the animals were put to death, and values for blood sugar and for muscle and liver glycogen were determined.

The results are reported in table 6. It will be noted that there is a definite decrease in liver glycogen in the experimental animals, no conclusions can be drawn about muscle glycogen. The figure for liver glycogen of the control is higher than is ordinarily reported for fasting animals, but it must be remembered that this rat received dextrose every four hours.

It was attempted next to study the effect of repeated injections of liver extract on carbohydrate stores of fed animals, in the same manner. Accordingly, 4 rats were made to fast for twenty-four hours, then for twelve hours they were fed 720 mg of dextrose per hundred grams of body weight every four hours (average maximum absorption of dextrose for this strain of rat) and given three injections of 0.67 cc of 14 per cent dextrose solution per hundred grams. At the end of this period, 1 animal, a control, continued to receive dextrose orally and by injection, while the others were fed dextrose but given injections of 0.67 cc of liver extract no. 1 per hundred grams of body weight. It was noticed that the experimental animals, which had hitherto tolerated the procedure well, became listless and weak, with poor muscle tone and depressed reactivity. The second feeding of dextrose and injection of liver extract intensified this state, in no case did an animal survive two injections. However, death was anticipated in the case of 1 animal and a determination of liver glycogen and blood sugar was made before it succumbed, a sample of muscle could not be obtained rapidly enough, unfortunately. The value for liver glycogen was 0.33 per cent, as against 6.0 per cent for the control animal.

The determinations of liver and muscle glycogen were made on animals that had fasted for twenty-four hours and received a single feeding of dextrose and one injection of liver extract. No controls were used, but one of the experiments was planned to duplicate the conditions under which Cori and Cori ¹⁵ studied the effect of epinephrine on carbohydrate stores in the postabsorptive state, the other simulated the experimental conditions under which Katzin ¹⁶

¹⁵ Cori, C. F., and Cori, G. T. The Mechanism of Epinephrine Action. II. The Influence of Epinephrine and Insulin on the Carbohydrate Metabolism of Rats in the Postabsorptive State, *J. Biol. Chem.* **79**: 321, 1928.
¹⁶ Katzin, R. The Role of the Adrenal Cortex in Carbohydrate Metabolism, Thesis, Yale University, 1940.

and Ferguson¹⁷ obtained normal values in the strain of rat used in this study

In the first experiment, a fasting rat was fed 720 mg of dextrose per hundred grams. At the end of a four hour absorption period, the animal was given an injection of 0.67 cc of liver extract no 1 per hundred grams. Three hours later it was killed, and liver and muscle glycogen were determined. The value for muscle glycogen, 0.54 per cent, checked well with Cori and Cori's figures for control animals, but that for liver glycogen, 2.0 per cent, was distinctly lower than their value, of 5.0 per cent.

In the second experiment, a fasting rat was given an injection of 0.67 cc of liver extract no 1 per hundred grams of body weight and one-half hour later fed 720 mg of dextrose per

period urine was collected (the bladders were expressed at the beginning and at the end of the twelve hours) and the animals were given injections of 0.67 cc of 14 per cent dextrose solution per hundred grams of body weight every four hours. At the conclusion of this control study, a second collection of urine over twelve hours was made, and the 2 experimental animals were given an injection of 0.67 cc of liver extract no 1 per hundred grams every four hours, while the control continued to receive dextrose. Thus 1 animal served as a control over the nitrogen excretion of the two twelve hour periods, whereas each experimental animal served as its own control during the foreperiod of twelve hours. The findings are reported in table 7. It was not expected that accurate

TABLE 7—*Urinary Excretion of Nitrogen Under the Influence of Liver Extract (Preliminary Fast of Twenty-Four Hours)*

Animal	First 12 Hours	Urinary Nitrogen, Mg	Urinary Nitrogen, Mg per Hour per 100 Gm	Second 12 Hours	Urinary Nitrogen, Mg	Urinary Nitrogen, Mg per Hour per 100 Gm	Nitrogen Deficit,* Mg per Hour per 100 Gm
S 9	0.67 cc 14 per cent dextrose solution per 100 Gm every 4 hours	58	3.0	0.67 cc 14 per cent dextrose solution per 100 Gm every 4 hours	54	2.8	0.2
S 8	Same as S 9	80	3.4	0.67 cc L. E. 1 per 100 Gm every 4 hours	106	4.5	2.5
S 10	Same as S 9	48	2.8	Same as S 8	100	5.8	0.6
S 11	720 mg dextrose solution per 100 Gm every 4 hours	33	1.4	720 mg dextrose per 100 Gm plus 0.67 cc 14% dextrose solution per 100 Gm every 4 hours	43	1.8	Excess of 0.4
S 12	Same as S 11	39	1.6	720 mg dextrose per 100 Gm plus 0.67 cc L. E. 1 per 100 Gm every 4 hours, died 5th hour	28	2.7	1.8*
S 13	Same as S 11	62	2.7	Same as S 12, died 5th hour	24	2.8	2.8*
S 14	Same as S 11	91	3.5	Same as S 12, died at 8 hours	50	2.9	4.2

* Nitrogen deficit = nitrogen excretion first 12 hours plus nitrogen in extract injected minus nitrogen excretion second 12 hours. The second injection was neglected in the case of S 12 and S 13, because death occurred shortly afterward.

hundred grams by stomach tube. At the end of four hours, the liver glycogen was 2.0 per cent and the muscle glycogen 0.42 per cent. In this case both muscle and liver glycogen are lower than Katzin's and Ferguson's figures for the normal rat under these conditions. It is noteworthy that the animal's blood sugar rose to 350 mg per hundred cubic centimeters.

Effect of Liver Extract on Nitrogen Balance—Studies of urinary nitrogen were performed to discover whether administration of liver extract caused any significant gluconeogenesis in addition to a mobilization of carbohydrate stores. Three normal rats were made to fast for twenty-four hours, in preparation for the first experimental period of twelve hours. During this

quantitative data would be obtained in this experiment, because of the relatively large amounts of nitrogen administered in the extract. However, it was felt that a significant gluconeogenesis should be revealed through the presence in the urine of excess nitrogen above that injected in the extract. This did not occur, in fact, a deficit of nitrogen was noted. This does not exclude the occurrence of gluconeogenesis, of course, since there is no evidence that the nitrogen in the extract is rapidly excreted.

It was hoped to throw further light on this question by repeating the experiment with dextrose-fed instead of fasting animals. In these circumstances gluconeogenesis would presumably be less likely to occur. Excess nitrogen found in the urine could then be taken as a rough measure of the excretion of nitrogen administered in the extract. Accordingly, an experi-

17 Ferguson, J. F., Jr. The Role of the Thyroid Gland in Carbohydrate Metabolism, Thesis, Yale University, 1940.

ment which has already been described was undertaken. Four animals after a preliminary test of twenty-four hours were fed 720 mg of dextrose per hundred grams of body weight every four hours and given an injection of 0.67 cc of 14 per cent dextrose solution per hundred grams every four hours, for twelve hours. The control animal continued to receive dextrose for the next twelve hours, whereas the experimental animals were fed dextrose but received injections of liver extract. However, as has already been reported, all the experimental rats went rapidly downhill and died after the second injection. Under these circumstances it is highly doubtful whether urinary excretion of nitrogen would have any validity as a control for the preceding experiment. The figures obtained are reported in table 7, although no conclusions are drawn from the data.

TABLE 8—Effect of Liver Extract on the Respiratory Quotient of Normal and of Diabetic Rats

Animal	R Q, Fasting	R Q, Fasting, Injections of Dextrose	R Q, Fasting, Injections of Liver Extract	R Q, Dextrose Feeding	R Q, Dextrose Feeding, Injections of Liver Extract
Normal					
S 21	0.72				
S 23	0.73			0.80 0.87 0.79	0.92 0.91
S 22	0.74				
S 6	0.73 0.74	0.75	0.83	0.79 0.87	0.91
S 5	0.73	0.75	0.79	0.87 0.87	0.92
Average normal	0.73	0.75	0.81	0.85	0.92
Depancreatized					
Y 128	0.75 0.74			0.79 0.72	0.75
Y 125	0.73 0.70			0.73 0.72	0.74
Average, de pancreatized	0.73			0.74	0.75

Dextrose feeding, 800 mg per hundred grams of body weight of rat. Injections, 0.67 cc of liver extract no. 1 or 14 per cent dextrose solution per hundred grams of body weight.

Effect of Liver Extract on Respiratory Quotients—Respiratory quotients of rats under the influence of liver extract were determined in the fasting state and during absorption of dextrose. The Haldane open circuit apparatus was used, as described under "Methods." In all trials rats were made to fast for twenty-four to thirty hours before the beginning of the experiment. Determinations were started one hour after feedings of dextrose and one-half hour after injections of liver extract or 14 per cent dextrose solution, they lasted two hours. The results are reported in table 8. It is seen that liver extract was capable of raising the respiratory quotient

of normal animals in either the fasting or the fed state but that there was no significant effect on the respiratory quotient of diabetic rats. The significance of these findings will be discussed later.

Some Properties of the Active Principle—Active liver extract was administered orally to mice and rats. A glycosuric response was obtained in both groups of animals. An effective dose for administration by stomach tube in the rat was about three times that which would produce an equivalent response if given parenterally, no quantitative data were obtained on mice.

The effect of heat on the activity of the extract was next investigated. It was found that neither of the two potent fractions lost any significant proportion of their activity on being maintained at 100 C for thirty minutes.

To study the effect of p_H on the activity of the liver extract, sulfuric acid and sodium hydroxide were added to two samples of liver extract no. 1, so that one sample contained 8 per cent acid by weight and the other 5 per cent alkali. The two solutions were then placed in a steam bath for fifteen minutes. After cooling, removal of the SO_4 ions and adjustment to neutrality, the two samples were compared in activity, the precautions outlined in the discussion of biologic assays being observed. It was found that the sample which had been incubated with acid was as active as before, while the one incubated with alkali had lost 40 per cent of its activity.

The active material was soluble in 60 per cent alcohol and was completely precipitated by 90 to 95 per cent alcohol. Its solubility in isopropyl alcohol was similar, but lower concentrations of this solvent served to cause precipitation. Centrifugation after such precipitations yielded a clear, deeply colored syrup of about one-fifth the volume of the original sample. None of the active principle was extracted from aqueous solution by butyl alcohol, acetone, chloroform or ether. The active material dialyzed somewhat slowly but completely through cellophane membranes.

Attempts at Fractionation of the Extract and Purification of the Active Principle—Although it was not expected that isolation of the active factor could be achieved in the time available, several attempts were made at fractionation of the extract. This was done for two reasons. First of all, the extract used was highly hypertonic and obviously irritating when injected, removal of inactive material would undoubtedly

produce a less hypertonic and probably a less irritating extract. Also, if it were possible either to separate the active principle from the reducing substance in the extract or to prove that the two were identical, problems of experimental technique, of interpretation and of assay and eventual purification of the active material would be made much simpler.

It was soon found that dialysis was of no assistance. The extract used was almost completely dialyzable. Fractional dialysis was attended with no success in separating the various components of the extract although theoretically this seemed an attractive tool.

Neither acid nor alkali precipitated any portion of the extract. Saturation with ammonium sulfate had no effect. Addition of the common organic solvents resulted in complete solubility, complete insolubility or uniform precipitation of the extract as the percentage of water in the solution decreased. When precipitation with ethyl alcohol was 50 per cent complete, activity and reducing power were found in both fractions. Recourse was next to various "precipitants." Addition to trimetaphenol had no effect. Tannic acid produced a small amount of precipitate. Lead, mercury and silver were found capable of precipitating large amounts of the material in the extract. Of these, mercury was somewhat capricious in its action, silver nitrate seemed to precipitate almost all the solid in the extract, while basic lead acetate removed about half of the solid material.

It was impossible to test biologically all the fractions prepared. The lead separation was therefore selected for trial, as it seemed certain that whichever fraction proved active, a twofold purification would have been achieved. This proved to be the case. The lead precipitate was regenerated by dissolving in nitric acid, removing lead with sulfate, and adjusting to neutrality, it was found to be inactive and to contain only a trace of reducing material. The lead filtrate, on the other hand, retained practically all of the activity and reducing power of the original extract.

The phosphotungstic acid precipitation that Cohn and associates¹⁸ found so useful in preparing pure preparations of the antianemic factor was now applied to the lead filtrate. This was acidified with sulfuric acid (to 5 per cent by weight), and 20 per cent phosphotungstic acid was added until precipitation was complete. The phosphotungstic precipitate was found di-

visible into alcohol-soluble, acetone-soluble and insoluble fractions. Material precipitated as phosphotungstate was regenerated with an excess of 20 per cent barium hydroxide, which removed phosphotungstate by precipitation as the barium salt. Injectable solutions of the various fractions obtained in this separation were prepared by precipitating toxic substances (phosphotungstate with barium, barium with sulfate) and adjusting to neutrality.

When the fractions obtained were tested biologically, in normal rats previously standardized with liver extract no 1, it was found that a considerable loss of activity had occurred during the separation. Neither the regenerated phosphotungstate precipitate nor any of its fractions were active. The phosphotungstate filtrate was

TABLE 9—*Fractionation of Active Liver Extract*

Fraction	Description	Reducing Power *	Activity
L E no 1	Control, known activity	++++	++++
3	Samples taken at various stages in the dialysis of liver extract no 1	+++ to ++++	+++ to
4			
5			
6			
7			
16	L E no 1 in 80% alcohol, precipitate	++++	++++
17	L E no 1 in 80% alcohol, supernatant	++++	++++
19	Filtrate after treatment of L E no 1 with basic lead acetate	++++	++++
23	Regenerated basic lead acetate precipitate	+	±
27	L E no 19 treated with phosphotungstic acid, regenerated precipitate	+	0
31	L E no 19 treated with phosphotungstic acid, filtrate	+++	++
40	L E no 31 in 50% alcohol, filtrate	+++	++
42	L E no 40 in 90% alcohol, precipitate	++	++++

* Correction is made for dilution undergone in the course of the fractionation.

active, but only weakly so. Most of the reducing material remained in the filtrate, there was some loss of this also.

The phosphotungstate filtrate was further purified by adding an equal volume of absolute alcohol and discarding the precipitate obtained, and then adding more alcohol until a 90 per cent alcohol mixture was obtained. On centrifugation, a small amount of clear golden liquid was obtained. This was dissolved in water and found to be active. Unfortunately, enough of this material was not available for quantitative estimation of reducing power. From the qualitative test, however, it seemed that, although there was some reduction, it was considerably less than usually obtained with this degree of activity.

Table 9 summarizes the positive results obtained in these attempts at fractionation of the

¹⁸ Cohn, E. J., and others. The Nature of the Material in Liver Effective in Pernicious Anemia, *J Biol Chem* **77** 325, 1928.

extract Under "description" are listed only the definitive steps of the fractionation. Fractions were of course freed of toxic material and reduced to neutral aqueous solution before injection. Correction is made for the effects of simple dilution.

Pathologic Studies—All animals used in this study were subjected to autopsy, either after natural death or at the conclusion of an experiment. No constant pathologic change was seen.

Sections of thyroid, heart, lung, spleen, kidney, adrenal and testis were taken from representative animals. Except for occasional pneumonic infiltration, no deviation from the normal microscopic appearance of these tissues was noted.

COMMENT

Glycosuria, Hyperglycemia and Glycogenolysis—It has been definitely established that injection of liver extract into normal rats causes glycosuria, hyperglycemia and a fall in the level of liver glycogen. The glycosuria is undoubtedly a reflection of the hyperglycemia, it is confined to the first few hours after the injection, when the blood dextrose is above the renal threshold, it is not excessive in amount.

A categorical explanation of the hyperglycemia is a little more difficult. Several factors may play a role in the production of this phenomenon. There is no doubt that the concomitant breakdown of liver glycogen accounts for an important share of the increased blood dextrose, especially in the postabsorptive state. This is not enough, however, for discharge of all the liver glycogen in a fasting rat would not produce enough dextrose to raise the concentration in the body fluids to the levels found. Two other intrinsic sources of dextrose are available to the rat, one extrinsic source is unwillingly supplied him. It can be shown that in the fasting rat maximal discharge of liver glycogen plus utilization of all the carbohydrate supplied in the liver extract is still not enough to account for the dextrose produced. Either gluconeogenesis or discharge of muscle glycogen must be postulated.

Carbohydrate balances have not been reported in this study because the differences in the muscle glycogen values obtained are not statistically significant. It is possible, however, by making an approximate balance sheet, to account for the dextrose mobilized by assuming a breakdown of muscle glycogen in addition to utilization of injected carbohydrate and mobilization of liver glycogen. This is entirely in accord with the

experimental data, for some decrease in muscle glycogen was actually observed. It can be stated, then, that at least in some animals liver extract produces a breakdown of both muscle and liver glycogen.

Gluconeogenesis—No evidence has been obtained that liver extract stimulates gluconeogenesis, all the experimental results can be explained without assuming this phenomenon. On the other hand, it has not been demonstrated that gluconeogenesis does not occur. Clarification of this issue must await at least partial purification of the liver extract and accumulation of further data on muscle glycogen.

Ability of the Tissues to Metabolize Dextrose—It has been demonstrated that administration of liver extract causes a rise in the respiratory quotient of normal animals. This is prima facie evidence that the ability of the tissues to metabolize dextrose is not impaired. It is possible however, to obtain high respiratory quotients by another mechanism—through the production of an acidosis with blowing off of the carbon dioxide.

If the action of liver extract were through a shift in bicarbonate balance of the blood, either because of the liberation of lactic acid or as a result of some other factor, an effect should be observed in diabetic as well as in normal animals. This was not the case. On correction of the values obtained by subtracting the 0.01 increase in respiratory quotient noted in depancreatized rats, it is found that administration of liver extract caused a rise in respiratory quotient of 0.05 in fasting and of 0.06 in dextrose-fed normal animals. These increases are significant.

It is seen, therefore, that the respiratory quotients of rats unable to metabolize dextrose did not change, while the respiratory quotients of normal rats increased under administration of liver extract. It must, then, be concluded that liver extract does not affect (adversely at least) the ability of the tissues to metabolize dextrose. It is likely that the increased combustion of dextrose noted in the normal rats is simply an expression of the law of mass action, since dextrose levels in their body fluids were markedly increased.

Mechanism of Action—The problem now remains of the mechanism through which the action of liver extract takes place. It has already been pointed out that there is no diminution of the ability of the tissues to metabolize carbohydrate and that the effects observed can be accounted for by a discharge of liver and muscle glycogen.

This may take place as a result of one or more of the following possibilities

(a) The liver extract used may contain some toxic substance which affects in an unphysiologic manner the glycogen storehouse of the body. An example of this type of action is the disturbance of carbohydrate metabolism occasionally found in catarrhal jaundice

(b) The liver extract may contain or stimulate the release of some substance known to affect carbohydrate metabolism "physiologically." Thus, many chemicals (e.g., morphine) produce hyperglycemia through stimulation of the adrenal medulla

(c) The extract may contain or stimulate the release of some active substance not hitherto known to affect carbohydrate metabolism

The first of these possibilities seems unlikely, for if a toxin were being frequently administered it is probable that the organism would react either by developing an antibody to the foreign material or by gradually succumbing to its influence and manifesting signs of progressive toxicity. Furthermore, damage to the tissues involved might be demonstrable microscopically. However, this is not the case. Several animals were given repeated injections of liver extract for periods up to two hundred days (one quarter of their life span) without showing any alteration in the response to the extract or any sign of ill health. Furthermore, no constant histologic change could be found.

The second possibility is a much more probable one. Most drugs producing hyperglycemia do so through a stimulation of the adrenal medulla. However, there are certain important differences between the action of liver extract and that of epinephrine. Cori and Cori, after a thorough study of the action of epinephrine on carbohydrate metabolism,¹⁹ concluded that the effects of that substance are due to a decrease in the utilization of carbohydrate by the tissues and a marked breakdown of muscle glycogen to lactic acid. They found that, although liver glycogen diminishes in the first fifteen minutes after

an injection of epinephrine, the rate of glycolysis from lactic acid soon exceeds the rate of hepatic glycogenolysis, so that liver glycogen is normal at the end of one hour and considerably increased at the end of three or four hours. Liver extract, on the other hand, has been shown not to decrease utilization of dextrose by the tissues, to cause only a moderate decrease in muscle glycogen and to cause a striking decrease in liver glycogen three or four hours after injection. Furthermore, although Cori and Cori were able to produce a considerable hyperglycemia in fasting rabbits and in rats in the absorptive state, they failed to do so in fasting rats.

Two points may be raised in question of the complete validity of the arguments just stated. First, the subcutaneous injection of epinephrine in the Cori experiments may not be entirely comparable in its effects on glycogen stores to the constant stimulation of the adrenal medulla that may be exerted by liver extract. This may be the case, although it seems somewhat improbable. It is difficult to see how a difference in liberation of epinephrine could reverse an effect on the respiratory exchange. Secondly, the failure to obtain significant hyperglycemia in fasting rats given injections of epinephrine, as well as the increase in liver glycogen noted, may be related to the dose used rather than to any specific action of epinephrine. Again, this may be so, although it seems unlikely that a hormone which has a definite and well authenticated action on blood sugar and on carbohydrate stores should in these experiments be the mechanism of an entirely dissimilar effect. And while it is true that the rats treated in this study were not, strictly, fasting animals, it is difficult to see how the administration of 93 mg. of carbohydrate per hundred grams of body weight to an animal maintaining a respiratory quotient of 0.79 for several hours would explain a difference of 130 mg. per hundred cubic centimeters in blood sugar four hours later.

It must be concluded, therefore, that the action of liver extracts in these experiments is not similar to the action of epinephrine on carbohydrate metabolism as described in the literature. This conclusion is supported by the work of Buttner,¹ who obtained a hyperglycemic response on injection of liver extract into adrenalectomized animals.

Reports of substances other than epinephrine or drugs acting through the adrenals which mobilize glycogen stores and produce a striking hyperglycemia have not been encountered in a brief survey of the literature. It is suggested, therefore, that the actions reported in this study

¹⁹ Cori, C. F., and Cori, G. T. The Mechanism of Epinephrine Action. I. The Influence of Epinephrine on the Carbohydrate Metabolism of Fasting Rats, with a Note on New Formation on Carbohydrates, *J. Biol. Chem.* **79** 309, 1928, II. The Mechanism of Epinephrine Action. The Influence of Epinephrine and Insulin on the Carbohydrate Metabolism of Rats in the Postabsorptive State, *ibid.* **79** 321, 1928, III. The Influence of Epinephrine on the Utilization of Absorbed Glucose, *ibid.* **79** 343, 1928, IV. The Influence of Epinephrine on Lactic Acid Production and Blood Sugar Utilization, *ibid.* **84** 683, 1929, V. Changes in Liver Glycogen and Blood Lactic Acid After Injection of Epinephrine and Insulin, *ibid.* **86** 375, 1930.

are due to a substance not hitherto known to affect carbohydrate metabolism and acting specifically on the mechanisms of formation or breakdown of glycogen. It is hoped that future investigation will shed light on the physiologic processes involved.

Feeding of Dextrose and Injection of Liver Extract—Of 3 animals fed dextrose by stomach tube and given an injection of liver extract and four hours later again fed dextrose and given another injection of the extract, all died, 2 during the fifth hour and 1 during the ninth. Animals given repeated injections of liver extract but not fed remained well. The rats that were fed dextrose and given injections of the extract seemed well shortly after the first injection, when next seen, at the time of the second injection, they were listless and flabby and not as reactive as usually. After the second feeding and injection they rapidly grew weaker and were later found dead.

Autopsy of these rats revealed no evidence of peritonitis or any other consequence of an error in technic. Unfortunately, histologic sections were not obtained. Explanation of these mortalities will not be attempted until further studies are undertaken, but it is suggested that they may represent a fatal intensification of the disturbance in carbohydrate equilibrium which was produced by liver extract, similar perhaps (by analogy only) to the effect obtained by administering a large amount of carbohydrate to a diabetic patient in delicate equilibrium.

The Liver Extract—Some progress has been made in fractionation of the liver extract, and it is hoped that a much purer preparation will be available for future experiments. The relation between reducing power and biologic activity is not entirely clear, if the activity of fraction 42 is confirmed it should be easy to demonstrate

that the reducing substance and the glycogenolytic principle are separate entities. The nature of the reducing substance has not been definitely established, the formation of glucosazone and the resistance to fermentation indicate it to be fructose or mannose. It is hard to understand why either of these hexoses should be found in such concentrations in liver extract. Of the two, fructose is more probable as a tissue constituent.

Future Investigation—It is obvious that many of the problems discussed here will require further study. Experimentation will be continued along the following lines:

- 1 Purification of the glycogenolytic principle
- 2 Effect of liver extract on carbohydrate stores, with obtaining of enough data to make it possible to draw up a carbohydrate balance sheet
- 3 Effect of liver extract on the medullo-adrenalectomized animal
- 4 Effect of liver extract on the lactic acid content of the blood

SUMMARY AND CONCLUSIONS

The existence in some liver extracts of a substance, not identical with the antianemic factor, capable of producing glycogenolysis, hyperglycemia and glycosuria in the normal rat has been demonstrated. It has been shown that this principle does not depress utilization of carbohydrate by the tissues and that its action is therefore not similar to that of epinephrine.

The glycogenolytic principle is water soluble, heat stable, and dialyzable through cellophane. It is not a protein. It is less active when given by mouth than when introduced parenterally. It is resistant to acid, although it loses some activity in alkali. A partial purification has been accomplished.

Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM JULY 1943 TO JUNE 1944

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CHICAGO

(Continued from page 278)

DUODENUM

Diverticula—Warren and Emery²³⁷ review the literature on duodenal diverticula and report a study of 103 cases. No typical symptomatology was found. Diverticula in the first portion of the duodenum are usually of the false type, pockets associated in most instances with duodenal ulcer, those in the second portion are usually a true herniation of the mucosa through the muscular wall, a fair number of these containing inclusions of pancreatic tissue. In 4 of the cases there was evidence of inflammation within the sac. In a fifth case the diverticulum was surrounded by a phlegmonous inflammation, the patient died of a purulent meningitis, hepatitis and endocarditis, but the pathologist was unable to determine the relationship between these infections and the diverticulum. Pease discusses²³⁸ the indications for operation and describes a technic for the removal of pei-vaterian diverticula.

Obstruction—Morlock and Gray²³⁹ report the case of a girl aged 16, who had attacks of painless vomiting intermittently all her life until at operation there was found an internal herniation of the third portion of the duodenum through a small rent in the mesentery, with resultant obstruction and dilatation of the duodenum. Incomplete rotation of the ascending colon was also present. The patient was cured. McCarty and Present²⁴⁰ describe a mesenteric pouch hernia resembling a paraduodenal hernia and discuss the anatomy and clinical features of both types. Acute duodenal obstruction due to calcified tuberculous retroperitoneal glands is reported²⁴¹.

Cyst—A case of enterogenous cyst of the duodenum is added to the 9 previously reported in the literature²⁴².

Rupture—Johnson²⁴³ reports on retroperitoneal rupture of the duodenum resulting from blunt trauma with cure effected by operation and reviews 52 cases from the literature.

Cancer—Howard,²⁴⁴ in reviewing the literature of carcinoma of the duodenum, found 55 instances recorded in 117,433 autopsies, an incidence of 0.047 per cent. In 10,340 cases of carcinoma of the intestines the incidence of carcinoma of the small intestine was 1.47 per cent. Of 163 cases of carcinoma of the small intestine, involvement of the duodenum was found in 37 per cent, of the jejunum in 37 per cent and of the ileum in 28 per cent. In the duodenum carcinoma was found in the first portion in 34 per cent, in the second portion in 45 per cent, and in the third portion in 21 per cent. Carcinomas of the duodenum are generally conceded not to arise from preexisting ulcers, are seldom associated with polyposis, most commonly occur in a stenosing form and less frequently assume a polypoid structure. They metastasize late and then usually involve only adjacent tissues. Few symptoms are produced until the lumen of the duodenum becomes obstructed. In the first portion of the duodenum the symptoms simulate pyloric carcinoma, in the second portion they simulate carcinoma of the ampulla of Vater, with jaundice, fever and sepsis, in the third portion they are characterized by obstruction with bile in the gastric contents.

237 Warren, H. A., and Emery, E. S. Duodenal Diverticula with Special Reference to Their Symptomatology, *Gastroenterology* **1** 1085-1099, 1943.

238 Pearse, H. E. The Surgical Management of Duodenal Diverticula, *Surgery* **15** 705-712, 1944.

239 Morlock, C. G., and Gray, H. K. Congenital Duodenal Obstruction, *Ann Surg* **118** 372-376, 1943.

240 McCarty, R. B., and Present, A. J. A Mesenteric Pouch Hernia Simulating Paraduodenal Hernia, *Surg, Gynec & Obst* **78** 643-648, 1944.

241 Solis-Cohen, L., Levine, S., Skversky, N. J., and Zaslow, J. Acute Complete Duodenal Obstruction, *Am J Surg* **62** 290-292, 1943.

242 Orgias, R. Enterogenous Cyst of the Duodenum, *Brit J Surg* **31** 90-93, 1943.

243 Johnson, M. L. Traumatic Retroperitoneal Rupture of the Duodenum. Presentation of a Case and Review of the Literature, *Arch Surg* **48** 372-380 (May) 1944.

244 Howard, J. W. Carcinoma of the Duodenum, *Am J M Sc* **206** 735-746, 1943.

Brunschwig and Templeton,²⁴⁵ in discussing the roentgenographic diagnosis of neoplasms of the peripapillary region of the duodenum, emphasize irregularities in the duodenal outline, stiffness of the involved segment, changes in the mucosal markings and Flostber's "reversed 3" sign. Cohn²⁴⁶ reports 2 cases of carcinoma of the duodenum in which the diagnosis was made preoperatively on the roentgenologic demonstration of an abnormal mucosal pattern, in both the onset was insidious and asymptomatic until obstructive symptoms appeared, the cancer developed above the ampulla, and hence there was no jaundice.

Grove and Rasmussen²⁴⁷ report obstructive jaundice in a 59 year old man in whom a benign papilloma of ampulla of Vater the size of a walnut was found and removed at operation. Watson²⁴⁸ describes a carcinoma of the ampulla removed successfully in a two stage resection. A case of intrapapillary adenocarcinoma of the duodenum is added to the 46 already in the literature.²⁴⁹

A parapyloric duodenal adenocarcinoma simulated duodenal ulcer preoperatively and remained cured five years following operation.²⁵⁰ Child²⁵¹ reports a case of pancreaticoduodenal carcinoma with symptoms of one month's duration in which radical pancreaticoduodenectomy was performed in one stage. The patient remained relatively free of symptoms for fourteen months, at which time reexploration revealed massive recurrence of the tumor.

Sarcoma—Bisgard and Cochran²⁵² describe primary lymphosarcoma successfully resected, although the patient died three months later.

245 Brunschwig, A, and Templeton, F E. Roentgenographic Diagnosis of Neoplasms of the Peripapillary Region and Head of the Pancreas, *Radiology* **41** 438-443, 1943.

246 Cohn, I. Carcinoma of the Duodenum, *Ann Surg* **119** 342-350, 1944.

247 Grove, L, and Rasmussen, E A. Benign Papilloma of the Ampulla of Vater, *Am J Surg* **64** 141-143, 1944.

248 Watson, K. Carcinoma of Ampulla of Vater. Successful Radical Resection, *Brit J Surg* **31** 368-373, 1944.

249 Felsen, J, and Wolarsky, W. Primary Intrapapillary Adenocarcinoma of the Duodenum, *Arch Path* **36** 428-431 (Oct) 1943.

250 Burke, E, Perkel, L L, and Gnassi, A M. Duodenal Carcinoma, *Am J Surg* **62** 267-271, 1943.

251 Child, C G. Carcinoma of Duodenum. One-Stage Radical Pancreatico-Duodenectomy Preserving the External Pancreatic Secretion, *Ann Surg* **118** 838-842, 1943.

252 Bisgard, J D, and Cochran, R M. Primary Sarcoma of Duodenum. Resection with Head of Pancreas by One-Stage Whipple Operation, *Am J Surg* **61** 425-429, 1944.

Williams²⁵³ reports a case of leiomyosarcoma which perforated, resulting in peritonitis and death of a 30 year old woman thirty-six hours post partum. In McCullough's²⁵⁴ case a leiomyosarcoma was complicated by ulceration, sinus formation and metastatic abscesses of the liver, lungs and heart.

SMALL INTESTINE

Physiology—Miller,²⁵⁵ in reviewing the investigations carried on in his clinic by means of small intestinal intubation, discusses intestinal absorption and the effects of drugs and of intestinal obstruction on the motility of the small bowel. Hamrick²⁵⁶ describes a method for the introduction of the Miller-Abbott tube in which air is injected into the stomach through the tube to aid its passage into the duodenum. Gius and Racely²⁵⁷ describe a simple, easily constructed, portable suction device dependent on the fact that a tire pump will provide suction when the plunger is reversed and designed primarily for use with the Miller-Abbott tube. It is effective, is simple and can be managed almost entirely by the patient himself.

Van Liere and co-workers,²⁵⁸ in studying the effects of anoxia, found that the motility of the small intestine of dogs was unaffected by the partial pressures of oxygen between 80 and 43 mm of mercury and that of mice with pressures above 94 mm. In the colon, anoxia produced a diminution in the contractions of both the longitudinal and the circular muscles. The influence of various agents affecting the autonomic nervous system was studied by giving a powdered charcoal mixture to matched pairs of unanesthetized dogs by stomach tube, using one animal as a control and its mate as the experimental subject and killing both after an appropriate interval, to determine the distance the charcoal mixture had

253 Williams, M H L. A Case of Perforating Leiomyosarcoma of the Duodenum Associated with Parturition, *M J Australia* **1** 585-586, 1944.

254 McCullough, K. Leiomyosarcoma of the Duodenum, *New York State J Med* **44** 1248-1249, 1944.

255 Miller, T G. Observations on the Human Digestive Tract by Intubation, *Proc Chicago Inst Med* **15** 118-129, 1944.

256 Hamrick, W H. A Technic for Introducing the Miller-Abbott Tube, *U S Nav M Bull* **41** 1737-1742, 1943.

257 Gius, J A, and Racely, C A. A New Portable Suction Apparatus for Use with the Miller-Abbott Tube, *Surgery* **15** 574-578, 1944.

258 Van Liere, E J, Northup, D W, Stickney, J C, and Emerson, G A. The Effect of Anoxia on Peristalsis of the Small and Large Intestine, *Am J Physiol* **140** 119-123, 1943.

traversed the small intestine²⁵⁹ Ergotamine increased the motility of the small intestine 27 per cent and neostigmine 38 per cent

Ingelfinger²⁶⁰ has written a comprehensive review of the effect of drugs, endocrine substances and vitamins on intestinal motility Huidobro, Montero and Cuevas²⁶¹ found that nitroglycerin does not affect intestinal movements but amyl nitrate and, to a lesser extent, theophylline ethylenediamine decrease movement and tonus Pitressin and, to a lesser extent, neostigmine increase the spontaneous motility of the small intestine Atropine sulfate and morphine decrease the motor activity, and the latter slightly increases the tonus

Meyer and associates,²⁶² having reported in previous papers that the salivary, gastric and pancreatic secretions are diminished in the aged, proceeded to study intestinal absorption by means of the Althausen galactose absorption test At the end of thirty minutes the group with an average age of 20.5 years absorbed approximately 50 per cent more galactose than the group with an average age of 76.6 years After sixty minutes the values for the two groups were approximately the same, after ninety minutes the older group had the higher values, thus giving further evidence of the delay in absorption

Kajdi and Davison²⁶³ studied the specific gravity, surface tension, p_{H} , trypsin and amylase content and the rate of flow of the duodenal fluid in 9 infants with normal digestion, 1 suffering from sprue and 1 from acute diarrhea The patient with acute diarrhea had a pronounced reduction of duodenal trypsin and amylase In the others the surface tension of the duodenal contents was stable in spite of variations in the rate of flow and concentration of enzymes and bile acids Walker,²⁶⁴ in *in vitro* studies, found

that caffeine had no effect on the activity of the digestive enzymes ptyalin, pancreatic amylase, pepsin, trypsin and pancreatic lipase Coffee extract did not affect the digestion of casein by pepsin or trypsin, it increased the rate of digestion of starch by salivary and pancreatic amylase and retarded the digestion of olive oil by pancreatic lipase

Fink and Nasset²⁶⁵ have provided a method for the bioassay of enterocrinin, the hormone which excites the secretory glands of the intestine, the principal feature of the method being that it gives accurate and reproducible results quickly by precise treatment of the time factor A statistical analysis of data on 9 dogs shows a closer correlation between dose and response when the dose of enterocrinin is given without reference to the weight of the dog than when it is given on a per kilogram of weight basis Secretin, likewise, was found to give more uniform responses in different dogs if the same dose was given, regardless of body weight, whereas the vasodilators present in intestinal extracts are best expressed on a per kilogram basis Fink²⁶⁶ describes a procedure for obtaining highly potent preparations of enterocrinin The potency has been increased to over three hundred times that of the crude extract

Forster, Helm and Ingelfinger²⁶⁷ conducted experiments in order to determine whether or not action potentials could be elicited from the intact human intestine and, if so, whether these potentials could be correlated with mechanical evidence of contraction and with the electrical potentials of smooth muscle as determined in animal experiments In 1 patient with an ileostomy the contractions were observed directly and in 4 patients indirectly with use of a Miller-Abbott tube The electrical potentials correlated with the mechanical evidence of contraction and in all essential respects were similar to the activity of isolated preparations of smooth muscle

Radiosodium was employed as a tracer in measuring rates of sodium ion movement into and out of the gut at several levels in chronic surgically prepared segments of dog intestine²⁶⁸

259 Van Liere, E. J., Northup, D. W., and Stickney, J. C. The Influence of Agents Affecting the Autonomic Nervous System on the Motility of the Small Intestine, *Am J Physiol* **141** 462-465, 1944

260 Ingelfinger, F. J. The Modification of Intestinal Motility by Drugs, *New England J Med* **229** 114-122, 1943

261 Huidobro, F., Montero, E., and Cuevas, F. The Effect of Drugs on the Motility of the Jejunum in Normal Man, *Surg, Gynec & Obst* **78** 471-476, 1944

262 Meyer, J., Sorter, H., Oliver, J., and Necheles, H. Studies in Old Age. VII. Intestinal Absorption in Old Age, *Gastroenterology* **1** 876-881, 1943

263 Kajdi, L., and Davison, W. Chemical and Enzymic Studies of the Duodenal Contents of Infants, *J Pediatr* **23** 204-214, 1943

264 Walker, F. The Effect of Caffeine in Coffee Extract on the Activity of the Digestive Enzymes, *Am J Physiol* **139** 343-346, 1943

265 Fink, R. M., and Nasset, E. S. The Physiological Response to Enterocrinin Considered Quantitatively, *Am J Physiol* **139** 626-632, 1943

266 Fink, R. M. The Fractionation of Enterocrinin Preparations, *Am J Physiol* **139** 633-637, 1943

267 Forster, F. M., Helm, J. D., Jr., and Ingelfinger, F. J. The Electric Potentials of the Human Small Intestine, *Am J Physiol* **139** 433-437, 1943

268 Visscher, M. B., Varco, R. H., Carr, C. W., Dean, R. B., and Erickson, D. Sodium Ion Movement Between the Intestinal Lumen and the Blood, *Am J Physiol* **141** 488-505, 1944

Sodium ions move in both directions across the intestinal epithelium at measurable rates under all conditions studied. There is in general a descending aboral gradient in movement of sodium from blood to intestine, the movement being least in the colon. The same holds for movement in the intestine to blood direction, except that there is probably little difference between ileum and colon. The rates of movement both out of and into the gut are both positively correlated with the sodium ion concentration in the small intestine. The colon possesses a more efficient absorbing mechanism. The observations stress the importance of dynamic factors in determining the apparent permeability of living membranes.

Smith and Bergmenn²⁶⁹ describe the preparation of l-leucine-aminoexopeptidase from swine intestinal mucosa together with evidence of the presence in swine mucosa of enzymes that hydrolyze various glycines.

Further information regarding the amount of small intestine required for the preservation of life is provided by 2 cases described by Prioleau.²⁷⁰ In the first the patient survived the resection of 260 cm of small intestine and 31 cm of sigmoid colon followed by two subsequent major operations to reestablish the continuity of the bowel. In the second case the patient survived the removal of 354 cm of small intestine and 40 cm of sigmoid. The first patient, from whom approximately 40 per cent of the small bowel was removed, remained well, in the second, who lost an estimated 53 per cent of his small intestine, diarrhea, emaciation and edema developed and he died in four months. These observations are thus in accord with the view that the upper limit of tolerated resection is 50 per cent.

Roentgenology—Schatzki²⁷¹ points out that in all parts of the gastrointestinal tract except the small intestine the examination is performed by observing roentgenoscopically the actual filling of the organ in question and then by studying the partially or completely filled organ. In the small intestine this may be accomplished by introducing barium sulfate solution through a duodenal tube. The barium reaches the cecum in an average time of fifteen minutes. The advantages of the method are. The small intestine

is seen filled in its entirety, the actual filling of the small intestinal loops can be observed roentgenoscopically, dehydration of the barium mixture, as in the usual peroral examination of the small intestine, resulting in a lumpy incomplete filling of the ileum, does not occur, an adequate examination of the ileocecal valve and cecum can be made when a rectal enema is contraindicated, the time required for the examination is shorter than with the conventional method. The disadvantages of the method are. There are annoyances and difficulties associated with the introduction of the duodenal tube, the purpose of the examination is defeated if the filling of the small intestine takes place very slowly, due usually to reflux into the stomach, functional changes in the small intestine are best studied by the conventional examination. Cases in which the method is contraindicated consist of those cases in which a routine gastrointestinal examination is contraindicated, cases of suspected gangrene of the bowel and cases of active duodenal ulcer.

In 5 dogs hypoproteinemia and edema had no significant effect on the rate of intestinal absorption of galactose and aminoacetic acid.²⁷² Roentgenologic observation after the administration of barium sulfate showed in some of the roentgenograms of the small intestine during edema a moderate clumping of the barium and segmentation.

Anomalies—Grove²⁷³ reports duplication of the terminal ileum associated with two congenital diverticula. Glover and Garvin²⁷⁴ report intestinal obstruction in a newborn infant in whom three anomalies were found at operation. Adhesive bands constricting the duodenum and a loop of jejunum passing through a hole in the mesentery together caused the obstruction and were associated with a third anomaly, partial volvulus of the nonrotated cecum. Recovery followed relief of the obstruction. Dolton²⁷⁵ reports intestinal obstruction due to herniation through a mesenteric defect. Stock and Can-

272 Beams, A. J., Free, A. H., and Leonards, J. R. Experimental Hypoproteinemia and Edema. Studies of Intestinal Absorption and Intestinal Roentgenologic Characteristics, *Arch Int Med* **73** 397-402 (May) 1944.

273 Grove, E. W. Duplication of the Terminal Ileum. Report of a Case Associated with Two Congenital Diverticula, *South M J* **36** 735-736, 1943.

274 Glover, D. M., and Garvin, J. A. Multiple Jejunal Congenital Anomalies with Intestinal Obstruction, *Ohio State M J* **39** 734-735, 1943.

275 Dolton, E. G. Mesenteric Defects, *Brit J Surg* **31** 275-277, 1944.

269 Smith, E. L., and Bergmenn, M. The Peptidases of Intestinal Mucosa, *J Biol Chem* **153** 627-651, 1943.

270 Prioleau, W. H. Massive Resection of the Small Intestine. Report of Two Cases, *Ann Surg* **119** 372-376, 1944.

271 Schatzki, R. Small Intestinal Enema, *Am J Roentgenol* **50** 743-751, 1943.

non²⁷⁶ report on a 3 day old child with symptoms of intestinal obstruction found at autopsy to have a blind end of the small bowel 3 inches (7.5 cm) beyond the duodenojejunal flexure

Volvulus—Barbosa²⁷⁷ reports on volvulus of the entire small intestine treated by detorsion, with recovery

Intussusception—Good²⁷⁸ discusses the diagnosis of enteroenteric intussusception roentgenologically after administration of barium sulfate by mouth. The characteristic observations are gradual narrowing of the lumen of the bowel as it approaches the intussusception, pronounced narrowing of the lumen through the intussusception, retrograde filling of the space between the intussusceptum and the intussuscepiens, with the formation of a characteristic "concentric ring" or "spiral sheath" appearance, and a palpable mass coincident with a filling defect in the barium column. Though enteroenteric intussusception is usually secondary to some other lesion of the bowel, the latter is seldom identifiable by the examination. Good considers the administration of barium by mouth to be safe if a barium sulfate enema has excluded obstruction of the colon.

Gibbs and Sutton²⁷⁹ review 92 cases of intussusception in infants and children observed over sixteen years. Scott²⁸⁰ presents a case of jejunal intussusception, thought to be the second in the literature. The patient was a 6 day old infant, with vomiting and passage of blood by rectum. Clark²⁸¹ reports on an irreducible double intussusception due to an invaginated Meckel diverticulum complicated by volvulus of the affected portion of bowel. Leiter²⁸² reports ileoileal intussusception due to a Meckel diverticulum in a 14 year old boy. Recovery followed resection of the intussusception with ileotransverse colostomy.

276 Stock, F. E., and Cannon, D. A. Atresia of the Small Intestine, *Brit J Surg* **31** 96-97, 1943

277 de Castro Barbosa, J. Volvulus of the Entire Small Intestine and Its Mesentery, *Am J Surg* **64** 400-404, 1944

278 Good, A. C. Enteroenteric Intussusception, *Radiology* **42** 122-127, 1944

279 Gibbs, E. W., and Sutton, P. W. Intussusception—Ninety-Two Cases in Infancy and Childhood, *Surgery* **14** 708-718, 1943

280 Scott, E. P. Jejunal Obstruction. Report of a Case in a Six-Day-Old Infant, *J Pediat* **23** 565-567, 1943

281 Clark, C. W. Irreducible Double Intussusception Due to Meckel's Diverticulum Complicated by Volvulus, *Brit J Surg* **31** 301-303, 1944

282 Leiter, H. E. Intussusception Due to Meckel's Diverticulum. Recovery Following Resection and Ileotransverse Colostomy, *J Mt Sinai Hosp* **10** 789-791, 1944

Stenosis and Adhesions—A 61 year old man with episodes of abdominal pain accompanied with nausea and vomiting was found at operation to have a strangulated bowel²⁸³. It was freed of adhesions, but the attacks of abdominal pain continued. At the second operation the stenosis was found to be caused by cicatricial tissue involving 8 cm of the bowel. Henry²⁸⁴ records a 30.6 per cent mortality in 219 cases of nonmalignant intestinal obstruction. In 77 cases simple release of adhesions resulted in a 15.5 per cent mortality. In 29 cases enterostomy for decompression was carried out, with a 41.4 per cent mortality. In 35 cases resection was necessary, the mortality being 57 per cent.

Bezoar—A trichobezoar in the terminal portion of the ileum resulted in volvulus, infarction of the bowel, peritonitis and death in a 13 year old girl²⁸⁵.

Rupture—Ficarra²⁸⁶ reports 16 interesting cases of nonpenetrating abdominal injuries with traumatic perforation of the small intestine.

Aneurysm—Hiller and Johnson²⁸⁷ review the literature of rupture of abdominal aneurysms in the intestinal tract and report on a 76 year old white man who complained for six weeks of constant epigastric pain, anorexia, intermittent nausea and abdominal distention. The guaiac test of the stools gave positive results on several examinations, the result of a roentgenologic examination of the gastrointestinal tract was reported negative. The patient suddenly became semicomatose, passed large amounts of blood by rectum and died. An arteriosclerotic aneurysm of the abdominal aorta perforating into the jejunum was present at autopsy.

Gallstone Ileus—Rankin and Eger²⁸⁸ report 3 cases of intestinal obstruction due to gallstones. In 2 the obstruction was high in the jejunum and in the third at the ileocecal junction. Nitkin

283 Tanner, N. C., and Bratton, A. B. A Case of Intestinal Stenosis Following Strangulation with a Pathological Description, *Brit J Surg* **31** 88-90, 1943

284 Henry, M. J. Non-Malignant Intestinal Obstruction, *South M J* **37** 69-72, 1944

285 Forbes, R. P. Bezoar Causing Intestinal Obstruction, *J Pediat* **24** 574-576, 1944

286 Ficarra, B. J. Traumatic Perforations of the Small Intestine Due to Non-Penetrating Abdominal Injuries, *Surgery* **15** 465-475, 1944

287 Hiller, G. I., and Johnson, R. M. Abdominal Aortic Aneurysm Rupture into the Jejunum Preceded by Occult Blood in the Stool, *Am J M Sc* **207** 600-606, 1944

288 Rankin, L. M., and Eger, S. A. Intestinal Obstruction Due to Gallstone, *Am J Surg* **61** 445-448, 1944

and Lesser²⁸⁹ describe intestinal obstruction due to gallstone with preoperative roentgen visualization of the biliary radicles. Of 36 such roentgenologically studied cases previously reported in the literature visualization of the biliary tract was observed preoperatively in 22. The following signs of gallstone ileus are recognized: air or contrast medium in the biliary tract, complete or partial intestinal obstruction as noted by distended loops of bowel, with visualization of the stone by a plain film or by the ingestion of a barium sulfate meal permitting the outlining of a radiolucent calculus, change in position of a previously observed stone. Utilization of intestinal intubation preoperatively contributes materially to the management in such cases by decompression of the bowel and by permitting the administration and subsequent removal of barium for the identification of the obstruction.

A 74 year old woman with a history of biliary colic after five days in the hospital for biliary colic had sudden acute pain in the lower part of the abdomen followed by symptoms of acute intestinal obstruction.²⁹⁰ The Miller-Abbott tube was passed, the general improvement was so striking that operation was not performed. Roentgenologic examination showed a stone in the colon and later two big stones were passed in the stools. Gastroduodenal roentgenograms disclosed a cholecystoduodenal fistula.

Diverticula—Benson, Dixon and Waugh²⁹¹ present results of an interesting study of 122 cases of so-called nonmeckelian diverticula, in 100 occurring in the jejunum, in 17 in the ileum and in 5 throughout the intestine. Symptoms developed only when complications occurred, as they did in 13 cases, chronic intestinal obstruction being the most frequent complication. The first case of carcinoma of a jejunal diverticulum is reported. D'Abreu²⁹² reports the unusual case of a 37 year old man with epigastric pain after meals, relieved by alkalis and aggravated by meat, associated with colic-like abdominal pain and alternating diarrhea and constipation. At operation a huge diverticulum of the small bowel was found at the junction of the jejunum and the ileum.

A Meckel diverticulum 18 inches (46 cm) from the ileocecal valve was visualized by a barium sulfate enema.²⁹³ Calcified concretions are described in a Meckel diverticulum.²⁹⁴ The tip of the diverticulum was attached to the tip of the appendix, forming a band that caused mechanical obstruction. Rudder²⁹⁵ reports acute diverticulitis of the jejunum, with resection and uneventful recovery.

Treatment of Intestinal Obstruction—Grimson and Hodge²⁹⁶ discuss the use of prolonged intubation suction technic in the treatment of intestinal obstruction produced by postoperative or inflammatory adhesions and present 7 cases illustrating the success of this method. However, patients with strangulation or recurring attacks of obstruction in spite of conservative treatment require exploration. Bennett²⁹⁷ also discusses the diagnosis and treatment.

Sprue and Related Disorders—Crohn²⁹⁸ reviews the recent advances made in the study of the diseases of the small bowel, including sprue, the deficiency states, ileojeunitis and regional enteritis. Sprue is interpreted by Wilder²⁹⁹ as one type of jejunoileal functional insufficiency with diminution in absorption of the products of digestion as well as of minerals and vitamins. Since fats are less readily absorbed than proteins or carbohydrates in normal persons, it is readily understandable that inadequate absorption of fat should be responsible for many of the symptoms. The excessive amounts of split fat and soaps in the stools are characteristic. In the active stages of the disease fat in the form of fatty acids and soap may constitute 50 per cent or more of the dried weight of the stool. Lack of absorption of fat causes serious deficiencies of all the fat-soluble vitamins, A, D and K, and excessive loss

293 Poppel, M. H. The Roentgen Demonstration of Meckel's Diverticulum, *Am J Roentgenol* **51** 205-206, 1944.

294 Gile, J. F., and MacCarty, W. C. Calcified Concretions Within a Meckel's Diverticulum, *Radiology* **41** 491-494, 1943.

295 Rudder, F. F. Acute Diverticulitis of the Jejunum—Case Report, *Surgery* **14** 921-923, 1943.

296 Grimson, K. S., and Hodge, G. B. Prolonged Intubation Suction and Deferred or Delayed Surgery in the Treatment of Multiple Adhesive Obstructions of the Small Intestine, *Surg, Gynec & Obst* **78** 316-326, 1944.

297 Bennett, L. C. Diagnosis and Treatment of Obstruction of the Small Intestine, *Am J Surg* **62** 59-64, 1943.

298 Crohn, B. B. Benign Diseases of Small Intestine, *Gastroenterology* **2** 385-394, 1944.

299 Wilder, R. M., Jr. The Nontropical Sprue Syndrome. Report of Four Cases and of a Case in Which Intestinal Insufficiency Was Corrected by Operation, *Proc Staff Meet, Mayo Clin* **19** 297-302, 1944.

289 Nitkin, R. L., and Lesser, A. Intestinal Obstruction Due to Gallstone, *Ann Surg* **118** 101-106, 1943.

290 Owens, F. M., Jr. Gallstone Ileus. Successful Treatment with the Miller-Abbott Tube, *Gastroenterology* **1** 938-941, 1943.

291 Benson, R. E., Dixon, C. F., and Waugh, J. M. Nonmeckelian Diverticula of the Jejunum and Ileum, *Ann Surg* **118** 377-393, 1943.

292 d'Abreu, F. An Unusual Case of Diverticulum of the Small Intestine, *Brit J Surg* **31** 408-409, 1944.

of calcium in the stools. Delayed absorption of dextrose causes a flattened curve in the dextrose tolerance test. Likewise, vitamin B complex, vitamin C and iron are poorly absorbed. Four typical cases are described, with prompt response to a low fat diet and large doses of minerals and vitamins. A fifth and very instructive case is one in which a gastroenterostomy had inadvertently been done between the stomach and lower part of the ileum, with resultant fatty diarrhea (62 per cent of the dry weight) and low level of plasma vitamin C. Prompt recovery occurred after the gastroenteric stoma was taken down. Adlersberg and Sobotka³⁰⁰ have also called attention to the inability of the small intestine to absorb fat and the fat-soluble vitamin A during an attack of sprue whereas during a remission after adequate treatment there is fairly satisfactory absorption of both. The fat tolerance and vitamin A absorption tests are described in four groups of patients: control, with active sprue, with inactive sprue and with jejunoileitis.

McIntosh,³⁰¹ in discussing the disorders of the digestive system leading to vitamin deficiency, states that the failure of absorption of fat-soluble vitamins A and K, and to a less extent vitamin D, occurs in diseases with jaundice and acholic stools, in fibrosing pancreatitis and in celiac disease. Fibrosing pancreatitis, often mistaken for celiac disease, is differentiated from it by the demonstration of an absence of the normal pancreatic enzyme from the duodenal contents under controlled conditions. Hence, if the examination of the stool for fat discloses a significant degree of impaired fat absorption, one must be prepared to go ahead with procedures leading to a more certain appraisal of pancreatic performance.

In an effort to classify recurrent and chronic diarrhea of infancy and childhood, the type of metabolic diarrhea known as the "celiac syndrome" has been divided by the Lapin³⁰² into five subtypes, namely: cystic fibrosis of the pancreas, intolerance to starch, infantile steatorrhea, celiac disease and allergic celiac disease. The evidence supporting this differentiation is not entirely satisfactory to us, but the emphasis on quantitative chemical analyses of the stool for fat and starch is amply justified.

300 Adlersberg, D., and Sobotka, H. Fat and Vitamin A Absorption in Sprue and Jejunoileitis, *Gastroenterology* **1** 357-365, 1943.

301 McIntosh, R. Disorders of the Digestive System Leading to Vitamin Deficiency States in Infants and Children, *Bull New York Acad Med* **20** 25-33, 1944.

302 Lapin, J. H. Recurrent and Chronic Diarrhea in Infancy and Childhood, *Am J Dis Child* **67** 139-143 (Feb.) 1944.

Fritzsche³⁰³ reports on lymphosarcomatosis of the small intestine and of the mesenteric lymph nodes in which the clinical picture was that of endemic sprue with chronic fatty diarrhea, swelling of the abdomen, emaciation, mild anemia of the secondary type and roentgenologic evidence of a severe jejunitis, ileitis and colitis. The disturbance in the absorption of fat was apparently explained by the extensive infiltration in the small intestine, particularly the jejunum and upper portion of the ileum and in the mesenteric lymph nodes.

Morlock and Rosenberg³⁰⁴ report the unusual association of nontropical sprue and severe tophaceous gout.

Forbes and Atkinson³⁰⁵ describe a relatively simple titration method for the determination of neutral fat, including sterols, and of the fatty acids, including both fatty acids and soaps, in the feces. Volk and Popper³⁰⁶ urge use of the fluorescent microscope for the demonstration of fat droplets in urine and feces as a better and simpler method than staining with sudan III.

Regional Enteritis—The perplexing problem of regional enteritis is well discussed in a recent editorial.³⁰⁷ Pathologically the distinguishing features are: 1 Hypertrophy and thickening of the wall of the bowel, usually confined to some one localized stretch of the mesenteric small intestine, most frequently the terminal ileum, and varying in extent from a few inches to several feet. A bizarre feature of the disease is its occasional tendency to attack more than one segment of the bowel, leaving the intervening segments intact. The process may involve the colon down to the sigmoid. 2 Resultant narrowing of the lumen of the bowel. 3 Hyperplasia of the mucosa, often with ulceration. 4 Perforation, with local or general peritoneal involvement and establishment of internal or external fistulas. This train of events is usually preceded by hyperplasia of lymphatic tissue and an obstructive

303 Fritzsche, R. Syndrom von symptomatischer Sprue bei Lymphosarkomatose des Dunndarms und der mesenterialen Lymphdrusen, *Schweiz med Wchnschr* **73** 442, 1943.

304 Morlock, C. G., and Rosenberg, E. F. The Coexistence of Tophaceous Gout and Non-Tropical Sprue. Report of a Case, *Ann Int Med* **20** 981-989, 1944.

305 Forbes, J. C., and Atkinson, T. T. The Separate Determination of the Fatty Acid Fraction and of the Neutral Fat Plus Sterol Fraction in Feces, *J Lab & Clin Med* **28** 1507-1510, 1943.

306 Volk, B. W., and Popper, H. Microscopic Demonstration of Fat in Urine and Stool by Means of Fluorescence Microscopy, *Am J Clin Path* **14** 234-238, 1944.

307 Regional Ileitis, editorial, *J A M A* **126** 499 (Oct 21) 1944.

lymphedema Microscopically the appearance is highly mimetic of tuberculosis, but all attempts to demonstrate tubercle bacilli or any other causative organism, including the virus of lymphogranuloma venereum, have failed The counterpart of the disease has not been observed in animals The diagnosis rests on symptoms so complex and varied as to create an almost invariable hazard Crohn's original classification of symptoms is valid today The disease may follow any of four patterns (1) that of acute intra-abdominal disease, resembling most frequently acute appendicitis, (2) that of ileocolitic diarrheal disease, (3) that of chronic intestinal obstruction with supervening acute obstruction, (4) that of fistula (external or internal) formation Differential diagnosis demands consideration of acute appendicitis, bacillary dysentery, acute perforative peritonitis, intestinal obstruction and cancer of the bowel Treatment is usually surgical However the disease frequently recurs after surgical removal of the grossly diseased segments and doubtless heals in many instances without resection

Holloway³⁰⁸ presents 13 well studied and illustrated cases to show the sequence of the gross pathologic changes in the acute, subacute and chronic forms The acute stage is characterized by pronounced edema attributed to lymphatic blockage and enlarged mesenteric nodes and accompanied with free intra-abdominal fluid The subacute stage consists in infiltration, exudation and engorgement with a tendency to perforation and fistula formation The chronic stage is manifested by stenosis, thickening and tumor formation The acute stage may subside completely, and hence conservative treatment is recommended In the chronic stage such resolution is unlikely, consequently short-circuiting procedures or resection are indicated Owens³⁰⁹ studied 22 cases and found neuromuscular hyperplasia to be a characteristic and hitherto unreported feature Fallis,³¹⁰ in reviewing 32 cases, noted that in 40.7 per cent of them the patients had previously had appendectomies and that 30 per cent of the patients undergoing resection required subsequent further resection

Wilensky³¹¹ gives an interesting description of a woman in the fifth decade of life who had

undergone an appendectomy twenty years earlier for "chronic appendicitis" Pain in the right lower quadrant of the abdomen recurred from time to time, becoming unusually aggravated in 1940 Roentgenologic examination showed the terminal segment of the ileum to be distorted and contracted for a distance of 5 inches (13 cm) The patient recovered and remained well The roentgenologic examination two years later showed no evidence of a lesion Wilensky interprets this as a case of nonspecific granuloma of the terminal ileum with spontaneous healing

Barnes³¹² describes an instance in which the terminal ileum, the ascending colon and part of the transverse colon were involved Resection of the terminal ileum and the right half of the colon has been performed for combined terminal ileitis and colitis³¹³ An unusual and interesting case with the diagnosis of regional enteritis of the ascending colon is reported and discussed by Dr Castleman, who emphasizes the significance of the presence of giant cells in the pathologic differentiation of this disease from chronic nonspecific ulcerative colitis³¹⁴ The report of Phillips³¹⁵ is unusual because the patient was a 62 year old white man

In a case of nonspecific enteritis involving Meckel's diverticulum, a fistula had developed after a previous appendectomy and right salpingo-oophorectomy³¹⁶ A perforation was found in the diverticulum Regional ileitis with concomitant ureteritis due to extrinsic pressure of the mass on the ureter is described³¹⁷ After removal of the focus of infection and obstruction in the intestines, the ureter returned to normal

In a 23 year old white man with extensive granulomatous jejunoileitis, a pronounced hypoproteinemia which responded only moderately to the injection of proteins and amino acids was observed³¹⁸ A deficiency in pancreatic amylase complicated the disease The oral administra-

312 Barnes, J P Nonspecific Granuloma of the Colon, Texas State J Med **39** 529-532, 1944

313 River, L P, Howser, J W, and Vaughn, A M Regional Ileitis Management of Combined Involvement of Distal Ileum and Distal Colon, Am J Surg **63** 118-123, 1944

314 Case Records of the Massachusetts General Hospital, Cabot Case 30172, New England J Med **230** 526-529, 1944

315 Phillips, J R Regional Enteritis, Am J Digest Dis **11** 197-198, 1944

316 Horn, R C, Jr, and Rhoads, J E Regional Enteritis Involving Meckel's Diverticulum, Ann Surg **119** 274-278, 1944

317 Hyams, J A, Weinberg, S R, and Allev, J L Chronic Ileitis with Concomitant Ureteritis Case Report, Am J Surg **61** 117-120, 1943

318 Killian, S T, and Ingelfinger, F J Nutritional Problems Presented by a Patient with Extensive Jejunoileitis, Arch Int Med **73** 466-471 (June) 1944

308 Holloway, J W Regional Ileitis, Ann Surg **118** 329-342, 1943

309 Owens, F M, Jr Regional Enteritis Pathological Study of Twenty-Two Cases, Arch Surg **48** 465-471 (June) 1944

310 Fallis, L S Regional Enteritis Case Reports, Am J Surg **62** 225-230, 1943

311 Wilensky, A O Spontaneous Healing in Nonspecific Granuloma of the Terminal Ileum, Rev Gastroenterol **11** 108-110, 1944

tion of a concentrated amylase was followed by a gain in weight, an increase in serum proteins and an apparent inhibition of the growth of *Monilia albicans* in the stools

Cyst—Rosenburg³¹⁹ reports on an enterogenous cyst of the ileocecal junction. The diagnosis may be suggested preoperatively by a palpable mass in the right lower abdominal quadrant. Pain from distention within the cyst is the most frequent symptom, but intestinal obstruction due to local pressure of the tumor and bleeding from an erosion of a blood vessel may occur. Marsupialization is recommended.

Timoney³²⁰ resected successfully a mucocele of the appendix with local implantation of pseudomyxoma peritonei.

Benign Tumors—Commenting on the rarity of benign neoplasms of the small intestine, Collins³²¹ analyzes 18 cases of neurofibroma collected from the literature and reports the case of a Negro man, aged 65 with symptoms of acute intestinal obstruction of forty-eight hours' duration and a history of a mass in his abdomen for one year. At operation a tumor the size of a grapefruit and with a twisted pedicle was found. Schottenfeld³²² presents a complete discussion of lipomas of the small intestine and ileum, including a review of the literature and report of 6 cases.

Gordon-Taylor³²³ reports on a myoma of the midintestine resected successfully and also the case of a 67 year old man who had unexplained recurrent high intestinal bleeding, with no abnormality found at operation. However, at the autopsy, performed a few days later, a tumor the size of a small orange was found in the middle of the jejunum. The tumor, ulcerated on its mucosal surface, was histologically a leiomyoma. In 1 of 2 cases recurrent melena was due to a leiomyoma of the terminal portion of the jejunum and in the second to a degenerating leiomyosarcoma of the midportion of the ileum.³²⁴

Golden³²⁵ reports that the ileocecal valve is rarely large enough to produce a recognizable indentation on the shadow of the barium-filled cecum, although it can sometimes be demonstrated on pressure films. Two cases are described in which the lips of the valve were enlarged. At operation hypertrophy of the lips of the valve with edema of the mucosa was found, the edema involving the terminal ileum and attributed to alcoholism with nutritional deficiency. In the second case the hypertrophy was also due to edema of the ileal side of the valve projecting into the cecum and producing early regional enteritis.

Carcinoid Tumors—In a study of 130 carcinomas of the small intestine 30 so-called carcinoid tumors were found.³²⁶ Thirteen of these had metastasized locally or distantly. Nine of the tumors were responsible for disabling symptoms, chiefly chronic intestinal obstruction. The lesions may occur anywhere from the esophagus to the anus, but they tend to be present in the terminal segments of the ileum as small orange submucosal nodules with minimal ulceration. Fifty per cent of the tumors were multicentric. Puckering and kinking were observed in the region of the tumor. Involvement of regional lymph nodes was observed in 11 and hepatic metastasis in 5. The term "little carcinoma" is apt, for large lesions are rarely encountered, although the metastatic deposits may be very large. Evidence is afforded that all carcinoid tumors are in essence peculiar low grade (1, Broders) adenocarcinomas. Nevertheless, it is suggested that the word "carcinoid" be appended by virtue of usage and as a designation of the peculiar mode of origin, life history and spread of these rather unusual neoplasms. They are always malignant, and metastasis occurs in at least a third.³²⁷ Two cases of carcinoid tumors of the ileum are reported,³²⁸ in both of which the symptoms of intestinal obstruction were present together with metastases to the regional lymph nodes. The unusual features in

319 Rosenberg, S. A. Enterogenous Cysts at the Ileocecal Junction, *Ann Surg* **119** 873-877, 1944

320 Timoney, F. X. Ruptured Mucocele of the Appendix with Pseudomyxoma Peritonei, *Am J Surg* **64** 417-419, 1944

321 Collins, J. D. Neurofibroma of the Small Intestine. Report of Case, *Ann Surg* **119** 362-371, 1944

322 Schottenfeld, L. E. Lipomas of the Gastrointestinal Tract with Special Reference to the Small Intestine Including the Ileum. Review of the Literature and Report of Six Cases, *Surgery* **14** 47-72, 1943

323 Gordon-Taylor, G. On Severe Intestinal Haemorrhage Due to Myomatous Tumour of the Jejunum with a Note on Bleeding Myomata of the Small Intestine, *Brit J Surg* **31** 266-269, 1944

324 Smith, L. A., Good, C. A., and Gray, H. K. Tumor of the Small Intestine as a Cause of Recurrent Melena, *Proc Staff Meet, Mayo Clin* **19** 117-122, 1944

325 Golden, R. Enlargement of the Ileocecal Valve, *Am J Roentgenol* **50** 19-23, 1944

326 Dockerty, M. B., and Ashburn, F. S. Carcinoid Tumors (So-Called) of the Ileum, *Arch Surg* **47** 221-246 (Sept) 1943

327 Dockerty, M. B., Ashburn, F. S., and Waugh, J. M. Metastasizing Carcinoids of the Ileum, *Proc Staff Meet, Mayo Clin* **19** 228-235, 1944

328 McLeod, C. E. Carcinoid Tumors of the Ileum (Argentaffinomas), *Am J Clin Path* **14** 301-303, 1944

the case of Korkosz³²⁹ are a spontaneous perforation of the ileum proximal to the site of the lesion and a general atrophy of the colonic mucosa associated with a submucous fatty replacement. A clinical diagnosis of terminal ileitis was corrected by microscopic examination to argentaffinoma of the ileocecal valve³³⁰.

A carcinoid tumor of the cecum with local and distant metastases is reported³³¹ in a 70 year old man, the fifth case of carcinoid tumor of the cecum in the literature.

Carcinoma—Boman,³³² in a paper on primary carcinoma of the jejunum and ileum, reviews the literature briefly and reports 7 interesting cases. Metastases to the mesenteric nodes were present in all and to the omentum and peritoneum in 1. Black³³³ reports ileoileocolic intussusception caused by a polypoid carcinoma of the ileum 40 cm proximal to the ileocecal valve. In 16,318 necropsies performed at the Cook County Hospital, Chicago, there were only 3 cases of primary carcinoma of the jejunum, including 1 intussusception³³⁴.

Sarcoma—A successfully resected sarcoma of the jejunum in association with von Recklinghausen's disease is described³³⁵. Though neurosarcoma occurs in 20 per cent of the cases of von Recklinghausen's disease, the occurrence in the jejunum is extremely rare. A malignant lymphoma with perforation of the small intestine is reported³³⁶.

APPENDIX

Acute Appendicitis—Etiology. In 61 cases of catarrhal appendicitis, Bowen³³⁷ found a stercolith in only 5 per cent, whereas in 63 cases with

gangrene it was present in 63 per cent, from this he concludes that in the severe grades of appendicitis the stercolith is clearly an important factor.

Diagnosis. Tripodi and Kruger³³⁸ report a case of appendical calculus recognized preoperatively by the presence of calcification in the right lower abdominal quadrant roentgenologically.

Shannon³³⁹ is of the opinion that obstructive appendicitis should be suspected in children who complain of repeated gastric upsets with abdominal pain, nausea and vomiting and that appendectomy should be performed before acute appendicitis develops. Globe³⁴⁰ distinguishes the generalized pain due to distention of the appendix from the localized pain due to irritation of the peritoneum. Hutchinson³⁴¹ reports bleeding from the inferior epigastric vessels in a 28 year old man with no history of trauma, in whom the symptoms suggested appendicitis. Myers and Rominger³⁴² report a retroperitoneal, retrocecal mucocele of the appendix of enormous size in a 72 year old patient. Newerla and Connally³⁴³ report a case of gangrenous appendicitis in a strangulated femoral hernia of the Richter type. River and Gradinger³⁴⁴ report appendiculocolic fistula with recurring attacks of pain in the right lower quadrant of the abdomen and a roentgenologic deformity of the cecum suggestive of neoplasm.

Hatchette³⁴⁵ describes left-sided appendicitis diagnosed entirely by roentgenologic examination, and confirmed by operation and pathologic examination. The incomplete rotation of the colon was not discovered until the roentgenologic examination. The pain was located in the left side of the abdomen, just above the level of the anterior iliac spine. On roentgenoscopic examination the proximal half of the transverse colon and a portion of the ascending colon were parallel to the distal half of the transverse colon and the

329 Korkosz. Malignant Argentaffinoma of the Ileocecal Valve, *Gastroenterology* **1** 961-964, 1943.

330 Case Records of the Massachusetts General Hospital, Cabot Case 30241, *New England J Med* **230** 739-742, 1944.

331 Potter, E. B., and Docter, J. M. Carcinoid Tumor of the Cecum, *Am J Path* **20** 143-147, 1944.

332 Boman, P. G. Primary Carcinoma of the Jejunum and the Ileum, *Ann Int Med* **20** 779-788, 1944.

333 Black, B. M. Polypoid Carcinoma of the Ileum Producing Intussusception. Primary Resection with Recovery of Patient, *Proc Staff Meet, Mayo Clin* **19** 142-146, 1944.

334 O'Donoghue, J. B., Lichtenstein, M. E. and Jacobs, M. B. Primary Adenocarcinoma of the Jejunum with Intussusception. Case Report, *Am J Surg* **63** 382-387, 1944.

335 Hamilton, J. B., Kennedy, P. C., and Herault, P. C. Neurogenic Sarcoma of the Jejunum Associated with von Recklinghausen's Disease, *Ann Surg* **119** 856-864, 1944.

336 Case Records at the Massachusetts General Hospital, Cabot Case 30011, *New England J Med* **230** 20-24, 1944.

337 Bowen, W. H. The Aetiology of Appendicitis, *Brit J Surg* **31** 127-135, 1943.

338 Tripodi, A. M., and Kruger, A. L. Appendiceal Lithiasis, *Am J Surg* **61** 138-142, 1943.

339 Shannon, W. R. The Crippled Appendix. A Pediatric Problem, *Minnesota Med* **27** 466-468, 1944.

340 Globe, R. A. Pain as a Symptom of Appendicitis, *Minnesota Med* **26** 622-624, 1943.

341 Hutchinson, W. B. Rectus Hemorrhage Simulating Appendicitis, *Northwest Med* **42** 16-17, 1944.

342 Myers, W. H., and Rominger, R. F. Retroperitoneal Mucocele of the Appendix. Case Report, *Am J Surg* **63** 362-367, 1944.

343 Newerla, G. J., and Connally, E. F. Gangrenous Appendicitis in Femoral Hernia of Richter's Type, *Am J Surg* **61** 154-156, 1943.

344 River, L. P., and Gradinger, B. C. Appendiculocolic Fistula. Report of a Case, *Am J Surg* **61** 297-299, 1943.

345 Hatchette, S. Roentgenologic Diagnosis of Left-Sided Appendicitis. Report of a Case, *Am J Roentgenol* **50** 244-247, 1943.

cecum lay parallel to the descending colon and anterior to it. The appendix filled well, was painful to pressure and contained a moderate-sized filling defect at the tip. At operation the tip of the appendix was included in an inflammatory process forming an abscess and involving also the mesentery of the small bowel of the left side. Since most reports in the literature state that the pain in left-sided appendicitis occurs on the right side, the location of the pain in this instance is ascribed to involvement of the mesentery. Prescott and Zollinger³⁴⁶ report 3 cases of acute appendicitis in situ inversus totale, in none of which the symptoms were referable to the right side.

Fraser,³⁴⁷ in a well documented historical, clinical, etiologic and pathologic study of intussusception of the appendix describes 7 instances of simple intussusception of the partial and complete types and refers to 82 cases in the literature. The characteristic clinical feature is the occurrence of very severe attacks of colic with periods of complete remission. Complete inversion of the appendix into the cecum may be associated with cecocolic intussusception and the appendix palpated at the rectum.³⁴⁸

Treatment—Behrend³⁴⁹ in reviewing 4,283 cases found that in 2,459 cases of acute appendicitis the mortality was 1.34 per cent. Apparently the mortality from appendicitis has been kept at a very low level in the last decade chiefly because of prompt diagnosis and operation and also because the number of interval and prophylactic appendectomies has reduced the number of possible cases³⁵⁰ of acute disease.

Spencer³⁵¹ reports 100 cases of suppurative and gangrenous appendicitis in patients treated in a small rural hospital with a mortality of 2 per cent. In 25 cases with perforation the mortality rate was 4 per cent. Chenoweth³⁵² reviews a series of 149 cases of appendiceal abscess. In

60 per cent the patients were subjected to appendectomy with drainage and in 40 per cent to incision and drainage only. The general mortality was 4.7 per cent. Of the patients whose appendixes were not removed either at the time of drainage or at a secondary elective operation 40 per cent had recurrent abscess.

In a review of 903 cases of perforative appendicitis both the morbidity and the mortality were reduced by the use of sulfonamide drugs, the mortality rate decreasing in the years from 1939 to 1942 from 9.2 per cent to 3.4 per cent as the use of sulfonamide compounds increased.³⁵³

DYSENTERY AND DIARRHEAL DISEASES

Epidemic Diarrhea of the Newborn—Geiger and Sappington³⁵⁴ report on an epidemic of diarrhea in the newborn infants, 324 cases with 45 deaths. Most of the patients were exposed apparently to infection during the first two weeks of life, and enteritis developed one to two weeks later. No definite etiologic factor was identified. Sakula³⁵⁵ studied an outbreak of gastroenteritis in the nursery of a maternity department in which 18 infants contracted the disease and 15 died, a mortality of over 80 per cent. The dissemination was confined to bottle-fed infants. The observations at necropsy suggested an acute toxic condition rather than an intestinal infection. *Pseudomonas pyocyanea* was isolated from the stools or elsewhere in 11 of the 25 cases.

Draper³⁵⁶ reports 22 cases of gastroenteritis in children under 5 years of age, *Bacillus typhimurium* being isolated from the stools in 20 and *Bacillus Reading* in 2.

Light and Hodes³⁵⁷ studied six separate epidemics occurring in three hospitals in the Baltimore-Washington area from the standpoint of a possible filtrable agent. In four of the epidemics a filtrable agent was isolated which regularly produced diarrhea in calves. This agent was not recovered from the stools of noi-

346 Prescott, M. U., and Zollinger, R. W. Appendicitis in Situs Inversus Totalis, *Am J Surg* **64**: 288-290, 1944.

347 Fraser, K. Intussusception of the Appendix, *Brit J Surg* **31**: 23-33, 1943.

348 McCrea, A. N., and Gans, B. A Case of Intussusception of the Appendix, *Brit J Surg* **31**: 197-198, 1943.

349 Behrend, M. Appendicitis. A Review of 4,283 Cases, *Am J Surg* **63**: 90-95, 1944.

350 Boone, H. R., and Lyons, S. C. The Mortality of Acute Appendicitis. Its Reduction by Diagnostic and Therapeutic Methods, *U S Nav M Bull* **41**: 1273-1283, 1943.

351 Spencer, J. H., Jr. Management of Acute Suppurative Appendicitis in the Small Rural Hospital. A Report of One Hundred Consecutive Cases, *Am J Surg* **61**: 249-258, 1944.

352 Chenoweth, A. I. Appendiceal Abscess, *Surgery* **14**: 702-707, 1943.

353 Stafford, C. E., Beswick, J., and Deeb, P. H. Evaluation of Sulfonamides in the Treatment of Peritonitis of Appendiceal Origin. A Review of 903 Cases of Acute Perforative Appendicitis, *Am J Surg* **64**: 227-234, 1944.

354 Geiger, J. C., and Sappington, E. E. Epidemic Diarrhea of the Newborn in San Francisco—1943, *Arch Pediat* **61**: 134-145, 1944.

355 Sakula, J. An Outbreak of Gastro-Enteritis in the Newborn, *Lancet* **2**: 758-760, 1943.

356 Draper, F. Gastroenteritis in Children. A Report on the Bacteriology of Twenty Cases Caused by Bacterium Typhi-Murium and Two Cases Caused by Bacterium Reading, *M J Australia* **1**: 533-539, 1944.

357 Light, J. S., and Hodes, H. L. Studies on Epidemic Diarrhea of Newborn. Isolation of a Filtrable Agent Causing Diarrhea in Calves, *Am J Pub Health* **33**: 1451-1454, 1943.

mal infants or normal calves. The evidence suggested, therefore, that the agent might be a cause of epidemic diarrhea of the newborn. Cultures of stool were uniformly negative for known diarrhea-producing organisms. The filtered stools were given by nasal inoculation. Successive passages through calves were found readily possible with each of the four strains, and the results of studies of cross immunity indicated that the four strains represented a single agent. The disease was produced in a total of 84 calves. Reimann, Price and Hodges³⁵⁸ studied an epidemic of diarrhea, nausea and vomiting of unknown cause, excluded food poisoning, found none of the usual bacteria or other parasites commonly associated with enteritis and attempted to isolate a filtrable infectious agent similar to that described by Light and Hodes, with negative results in the 8 experiments performed with fecal material preserved frozen with solid carbon dioxide for two months. Gunn³⁵⁹ reviews 411 cases of acute gastroenteritis. Glaser and Bruce³⁶⁰ report that in treatment the administration of unlimited amounts of butter milk, skimmed milk and protein milk decreased the period of hospitalization and the death rate.

Vitamin Deficiency—Wintrobe and his associates³⁶¹ found that pantothenic acid deficiency in young pigs was characterized by diarrhea, then dysentery and loss of appetite, striking impairment of growth, loss of hair, cough and excessive nasal secretion, changes in the tongue and abnormal gait. Extensive colitis was shown by hyperemia, edema and ready bleeding of the bowel when examined rectosigmoidoscopically. At autopsy the changes ranged from diffuse hyperemia with increase in the size of the lymphoid follicles and the formation of small ulcers to extensive inflammatory changes involving the entire intestine. Histologically, atrophy of the cells lining the glands of the mucosa, abscess formation and ulceration were observed. The administration of 500 or more micrograms of

calcium pantothenate per kilogram of body weight per day was accompanied with cessation of diarrhea, gradual improvement in the condition of the bowel, restoration of normal blood values, growth of hair and gain in weight.

Food Poisoning—Tapp³⁶² in reviewing the causes of food poisoning lists the following bacterial causes as *Salmonella*, *Staphylococcus* toxin and *Clostridium botulinum*, "milk sickness" due to trematol, a poisonous substance contained in weeds eaten by cattle and excreted in their milk, fungus poisoning, from inedible mushrooms, ergotism, from grain, mussel poisoning, and cadmium poisoning, from the metal used to plate cooking utensils. Hoechstetter³⁶³ discusses shellfish and mushroom poisoning. DeLay³⁶⁴ describes an outbreak of characteristic staphylococcal food poisoning in which enterotoxigenic staphylococci were obtained from a bread pudding served at the meal preceding the outbreak. About 400 of the 600 men served were affected. The pudding was allowed to stand at room temperature (75+ F) for over twenty-four hours. The outbreak illustrates the need for adequate facilities for refrigeration and their use.

Bacillary Dysentery—The most important of the diarrheal diseases, according to Callender³⁶⁵ is bacillary dysentery. Typhoid and the dysenteries ordinarily increase under the same unsanitary conditions. In the present war, however, typhoid vaccine appears to have controlled the incidence of this disease, while bacillary dysentery, for which no immunization has been developed, has risen in troops to heights equal to those of twenty years ago.

Hardy and Watt³⁶⁶ report on an excellent study carried out in Puerto Rico, New Mexico, Georgia and New York city. Satisfactory clinical data were obtained in 1,247 of 1,499 cases, with an epidemiologic history of 830 households. The term "shigellosis" is suggested for all infections due to pathogenic varieties of *Shigella*.

During the months of May, June and July 1943 an outbreak of acute enteritis occurred

358 Reimann, H. A., Price, A. H., and Hodges, J. H. Negative Results in Studies of Epidemic Diarrhea, Nausea and Vomiting of Unknown Cause, *Proc Soc Exper Biol & Med.* **55** 233-234, 1944.

359 Gunn, W. Acute Gastroenteritis in Children. A Review of 411 Cases, 1936-1943, and a Plan of Investigation and Treatment, *Brit J Child Dis* **41** 1-10, 1944.

360 Glaser, K., and Bruce, J. W. Treatment of Epidemic Diarrhea and Dysentery in Infants and Young Children, *J Pediat* **24** 53-61, 1944.

361 Wintrobe, M. M., Follis, R. H., Jr., Alcayaga, R., Paulson, M., and Humphreys, S. Pantothenic Acid Deficiency in Swine, with Particular Reference to the Effects on Growth and on the Alimentary Tract, *Bull Johns Hopkins Hosp* **73** 313-333, 1943.

362 Tapp, E. M. Food Poisoning, *M Bull Vet Admin* **20** 61-66, 1943.

363 Hoechstetter, S. S. Food Poisoning, *M Bull Vet Admin* **20** 58-60, 1943.

364 DeLay, P. D. Staphylococcal Enterotoxin in Bread Pudding, *Bull U S Army M Dept*, 1944, no 72, pp 71-73.

365 Callender, G. R. Dysenteries and Diarrheas. Their Importance in Military Service, *War Med* **4** 459-464 (Nov) 1943.

366 Hardy, A. V., and Watt, J. (a) The Acute Diarrheal Diseases, *J A M A* **124** 1173-1179 (April 22) 1944, (b) Newer Procedures in Laboratory Diagnosis and Therapy in the Control of Bacillary Dysentery, *Am J Pub Health* **34** 503-509, 1944.

among Army personnel stationed in North Africa. It was characterized by two types of enteritis, one mild and the other severe. The causative organisms were *Shigella paradysenteriae* (Flexner) 73 per cent, *Shigella ambigua* 11 per cent, unidentified paradysentery bacilli 9 per cent, *Shigella sonnei* 3 per cent, *Shigella madampensis* 2 per cent and *Shigella enteritidis* 2 per cent. The wide distribution of the *Shigella paradysenteriae* (Flexner) was proved by the fact that it was identified in other laboratories in other areas in North Africa. Gowen,³⁶⁷ on epidemiologic grounds, concludes that transmission by flies was probably the most important factor in the spread of the disease, although contact with carriers and persons with mild unrecognized forms of the disease undoubtedly played an important part once the troops had been seeded with the infection. Adams and Atwood,³⁶⁸ in a study of 251 cases of bacillary dysentery found shigella organisms in 90 per cent of the patients, salmonella organisms in 6 patients and an organism belonging to the paracol group in 33 patients. Of the shigella organisms found, 70.9 per cent were *Shigella paradysenteriae* and 8 per cent *Shigella Newcastle*. These responded to therapy with sulfonamide compounds. Twenty-eight infections due to *Shigella sonnei* and *Shigella alkaescens* did not respond to chemotherapy.

Bacillary dysentery occurs in Chicago as a sporadic disease throughout the year, with greater frequency in late summer and autumn months, 307 cases having been encountered at the Cook County Hospital during the years 1938 to 1941 inclusive.³⁶⁹ Some patients acting as "carriers" harbor the organisms over extended periods, in this series as long as seventy days. The mortality during the years 1938 to 1941 inclusive was 7 per cent, the majority of deaths occurring among the very old and the very young. Felsenfeld and Young,³⁷⁰ in 13,000 stool examinations of the state hospitals of the greater Chicago area, isolated 64 strains of *Salmonella* belonging to 19 types. Organisms were frequently found in symptomless carriers. Treat-

ment of the carriers with sulfonamide compounds resulted in failure. A number of dysentery infections were successfully treated with sulfadiazine and sulfathiazole, but those due to *Salmonella typhimurium*, the most common type, were resistant. A new three sugar medium has been devised³⁷¹ for the differentiation of *Salmonella* and paracol organisms. Littman³⁷² describes a rapid method for the isolation and identification of the enteric pathogenic organisms from the feces, utilizing standard mediums and generic charts of fermentative reactions and serologic characteristics. Larkum³⁷³ discusses the bacteriologic classification. Wheeler³⁷⁴ describes a method for the serologic identification of the pathogenic dysentery bacilli, utilizing a slide agglutination test, and presents the result of the serologic typing of 1,005 *Shigella* strains.

Acute dysentery in an infant 14 months of age is attributed to *Shigella alkaescens*.³⁷⁵ The pathologic changes were located primarily in the lymphoid tissue in the colon and in the ileum and contrasted with the diffuse involvement of the mucosa when Shiga and Flexner organisms are present. Attempts to infect animals were unsuccessful, although Edward did produce lesions in the rabbit almost identical to those seen in this case. Stuart and co-workers³⁷⁶ isolated from the stools of sick infants, normal exposed infants and normal adults having contact with the infants during an epidemic of gastroenteritis *Shigella alkaescens* and antigenically related organisms, forming an almost perfect intergrading series biochemically from *S. alkaescens* to *Escherichia coli*, thus suggesting their probably evolutionary development.

Seligmann and Heitz³⁷⁷ isolated fifteen different types of *Salmonella* in 37 cases observed at the Beth Israel Hospital. One or more types from each of the *Salmonella* groups was isolated.

367 Gowen, G. H. Acute Enteritis in North Africa, Bull. U. S. Army M. Dept., 1943, no. 71, pp. 55-58.

368 Adams, J. W., Jr., and Atwood, R. T. Bacillary Dysentery. A Bacteriologic and Clinical Analysis of 251 Cases Occurring in an Army Camp, War Med. 5: 14-20 (Jan.) 1944.

369 Chesley, F. F., and Woolsey, C. I. Frequency of Bacillary Dysentery at the Cook County Hospital, Chicago, Illinois, Gastroenterology 2: 258-264, 1944.

370 Felsenfeld, O., and Young, V. M. The Occurrence of Members of the Genus *Salmonella* in Inhabitants of State Hospitals of the Greater Chicago Area, J. Lab. & Clin. Med. 29: 375-382, 1944.

371 Felsenfeld, O., and Young, V. M. New Medium for the Differentiation of *Salmonella* and Paracol. Organisms, Am. J. Clin. Path. 14: 26-27, 1944.

372 Littman, M. L. Rapid Identification of the Enteric Pathogenic Bacteria, War Med. 4: 31-56 (July) 1943.

373 Larkum, N. W. Classification of the *Shigellas*, Bull. U. S. Army M. Dept., 1944, no. 72, pp. 106-110.

374 Wheeler, K. M. Serological Identification of Dysentery Bacilli, Am. J. Pub. Health 34: 621-629, 1944.

375 Rigdon, R. H., Michelson, I. D., and Allen, F. Acute Dysentery Produced by *Shigella Alkaescens*, Am. J. Trop. Med. 24: 135-140, 1944.

376 Stuart, C. A., Rustigian, R., Zimmerman, A., and Corrigan, F. Pathogenicity, Antigenic Relationships and Evolutionary Trends of *Shigella Alkaescens*, J. Immunol. 47: 425-437, 1943.

377 Seligmann, E., and Hertz, J. *Salmonella* Infections. Report of Thirty-Seven Cases Observed at Beth Israel Hospital, New York, in the Past Four Years, Ann. Int. Med. 20: 743-751, 1944.

in Florida³⁷⁸ A new *Salmonella* type obtained from the stool specimens of a normal food handler has been designated *Salmonella mississippi*³⁷⁹

Ferguson and Hook³⁸⁰ describe a method of distinguishing proteus and salmonella organisms by their growth on a medium containing urea, the proteus organisms decomposing the urea and the salmonella organisms showing no activity

Snapper,³⁸¹ in an analysis of the acute outbreaks of salmonella infections in Western Europe and also in the United States attributed to contaminated duck eggs, shows that the disease usually does not result directly from the ingestion of infected eggs, the number of organisms in any one egg being small, but rather is due to the infection of custards, puddings and other dishes in which growth and multiplication of the organisms occurs

Coughlin³⁸² describes a hotel outbreak of gastroenteritis affecting 83 persons, including 70 of the 78 persons attending a college alumni dinner, 10 of the 19 attending an insurance company's dinner, 2 members of the hotel staff and a guest at the hotel The infection was attributed to chef's salad prepared by the assistant chef, who was the only hotel employee who remained well and in whose stools *Salmonella derby* were found The evidence, however, was not conclusive Coleman, in discussing this paper, points out that more than 100 species of *Salmonella* are now recognized and suggests that while human carriers must be recognized as a potential source of infection, even though epidemiologic studies seldom indicate transmission from person to person, the frequency with which various salmonella organisms have been found in tissues from apparently normal as well as diseased animals and birds suggests that they constitute the main reservoir for human infection

An outbreak of milk-borne gastroenteritis due to *Salmonella dublin* affected 162 persons³⁸³ The source of the infection was traced to an apparently healthy cow excreting large numbers of the organisms An epidemic of sonne dysentery was due apparently to an infected water supply, as the bacillus was isolated from a sample of the water which had passed satisfactorily the usual bacteriologic tests after chlorination³⁸⁴ Hailwood³⁸⁵ describes an outbreak of Sonne dysentery spread by food infected by a chronic carrier who gave a history of diarrhea one year previously He was the only person whose stools contained *Bacillus dysenteriae* Sonne who was asymptomatic during the period of the epidemic Zellweger,³⁸⁶ in a study of an epidemic of bacillary dysentery (type Sonne-Kruse) occurring in soldiers in the field and attributed to the contamination of the food by flies, emphasizes the importance of prophylaxis because of the enormous disability occasioned by the epidemic

Ethylene glycol and phenol extracts of the Shiga bacillus produce considerable immunity in the mouse to infection with fully toxigenic strains of *Bacterium shigae*³⁸⁷ Large doses of formaldehyde-treated vaccine induce resistance to infection in mice almost as well as the extract but fail to elicit agglutinins to the same extent In an effort to find an agent which would be polyvalent and relatively nontoxic for the prophylactic immunization of human beings against dysentery bacilli infections, an antigen prepared from type V *Shigella paradysenteriae* was found to give rise in human beings to antibodies which are broadly cross reactive³⁸⁸ The toxic properties of the antigen are undesirable but apparently not prohibitive when the antigen is used in the small quantities required Whether it will afford protection against bacillary dysentery awaits trial in the field Age apparently is not

378 Galton, M M, and Quan, A L Varieties of *Salmonella* Isolated in Florida During 1942, *Am J Hyg* **38** 173-177, 1943

379 Edwards, P R, Cherry, W P, and Brunner, D W A New *Salmonella* Type *Salmonella Mississippi*, *Proc Soc Exper Biol & Med* **54** 263-264, 1943

380 Ferguson, W W, and Hook, A E Urease Activity of *Proteus* and *Salmonella* Organisms, *J Lab & Clin Med* **28** 1715-1720, 1943

381 Snapper, I Salmonellosis Caused by the Ingestion of Ducks' Eggs, *Am J Digest Dis* **11** 8-10, 1944

382 Coughlin, F E Hotel Outbreak of Gastroenteritis Due to *Salmonella Derby*, *New York State J Med* **44** 718-723, 1944

383 Berger, F M, and Sutherland, P L Milk-borne Gastroenteritis Due to *Salmonella Dublin* *Brit M J* **1** 488-490, 1944

384 Green, C A, and Macleod, M C Explosive Epidemic of Sonne Dysentery, *Brit M J* **1** 259-261, 1943

385 Hailwood, J G The Carrier State in Sonne Dysentery, *Brit M J* **2** 806-807, 1944

386 Zellweger, H Ueber Eine Dysenterie-Epidemie (Typhus Sonne-Kruse) in Artindienst, *Schweiz med Wchnschr* **24** 422-426, 1943

387 Schutze, H Extracts of *Bacterium Shigae* as Immunizing Agents in Mouse, *J Path & Bact* **55** 457-464, 1943

388 Goebel, W F, Perlman, E, and Binkley, F Antibody Response in Man to Injection of the Specific Antigen of Type V *Shigella Paradysenteriae*, *Science* **99** 412-413, 1944

a significant factor in susceptibility to the endotoxin of *S. paratyphenteriae*.³⁸⁹

D'Antoni³⁹⁰ distinguishes chronic bacillary dysentery in which there is a continuation of the dysenteric stools, with pus and blood, from *Shigella colitis*, in which there is only a diarrhea of liquid feces. In the latter the organisms may be difficult to demonstrate, 20 examinations of stools being required in some instances. In the 150 cases observed an average of 5 stool examinations were required before a positive diagnosis was made.

Felsenfeld,³⁹¹ with special reference to the *Monilia-Cryptococcus-Geotrichum* group of fungi, investigated the mycotic flora of the intestinal tract of institutionalized patients in an effort to find possible causes of enteric infections other than the common pathogenic bacteria and parasites. The first group of patients consisted of 300 newly admitted persons and 600 from the wards for chronic disease, all without intestinal disturbances. The second group consisted of 100 chronic typhoid carriers. The third group, composed of patients with diarrhea, was subdivided into these classifications: 47 in the early acute stage of *Shigella sonnei* and paratyphenteria infections, 51 with bacillary dysentery one week after termination of treatment with sulfathiazole, and 103 who had food upsets with diarrhea of short duration and without determinable cause. Of the newly admitted patients 26.6 per cent had no fungi. The three species of fungi were found in about equal numbers in the remainder, and in the majority only one species was present. In the patients from the chronic ward and the typhoid carriers there was some tendency to harbor two or three species. In the "food upset" group the incidence of *Geotrichum* doubled with a 50 per cent increase in the number harboring two species. In the group with bacillary dysentery the incidence of *Monilia* organisms increased. In the patients with dysentery treated with sulfathiazole there was an absolute and a relative decrease in the incidence of all three species of fungi.

Chemotherapy—Succinylsulfathiazole was given to 3 dysentery carriers in amounts of 0.147, 0.195 and 0.220 Gm per kilogram of body

weight daily.³⁹² These amounts did not successfully eliminate the organisms from the stools when given for seven days, but when given for fourteen days they did so. A fourth patient did not respond to 0.166 Gm of the drug per kilogram daily for fourteen days but was rendered free from dysentery bacilli by 0.25 Gm per kilogram daily for five days. A fifth patient recovered spontaneously from the carrier state. Although relatively small amounts of succinylsulfathiazole are effective if continued for a long time, a dosage of 0.25 Gm per kilogram daily for five to seven days should uniformly eliminate dysentery bacilli from the stools of carriers in a short time.

In an outbreak of Sonne dysentery involving 50 children in an orphanage with a total census of 145, organisms were found in the stools of 83.³⁹³ The administration of sulfathiazole and sulfadiazine in doses of 1 grain (0.06 Gm) and sulfaguanidine and succinylsulfathiazole in doses of 2 grains (0.13 Gm) per pound (0.5 Kg) of body weight cleared 90 per cent of the positive stools in four days. The remaining 10 per cent were cleared with one or two additional courses of treatment. The administration of the drugs caused complete inhibition of growth of intestinal bacteria for a time in 80 per cent of the persons treated with sulfadiazine, 63 per cent of those treated with succinylsulfathiazole and 37 per cent of all treated with sulfaguanidine.

Sulfaguanidine has been used during the early convalescent stage of Sonne bacillary dysentery in an attempt to shorten the carrier state; the attempt was unsuccessful when one fourth of the therapeutic dose was given daily, but in another experiment in prophylaxis 2 Gm daily for ten days given to thirty-six persons at the outset of an epidemic apparently prevented dysentery, whereas of 45 persons used as controls 9 contracted the disease.³⁹⁴ Smith³⁹⁵ treated 44 young women, mainly symptomless carriers of *Bacillus dysenteriae* (Flexner), with massive doses; the bacteriologic results were satisfactory, but in 21 of them a toxic rash developed on about the ninth day of treatment. Eight of 12 patients

389 Zahl, P. A., Hutner, S. H., and Cooper, F. S. Age as a Factor in Susceptibility of Mice to the Endotoxin of Bacillary Dysentery, *Proc Soc Exptl Biol & Med* **54** 137-139, 1943.

390 D'Antoni, J. A. Bacillary Dysentery, with Special Reference to the Chronic Form (*Shigella Colitis*), *Clinics* **2** 936-954, 1943.

391 Felsenfeld, O. Yeast-like Fungi in the Intestinal Tract of Chronically Institutionalized Patients, *Am J M Sc* **207** 60-63, 1944.

392 Barker, P. S. The Treatment of Dysentery Carriers with Succinylsulfathiazole. Observations on the Minimal Effective Dose, *Am J Digest Dis* **10** 443-444, 1943.

393 Eisenoff, H. M., and Goldstein, H. The Control of an Outbreak of Bacillary Dysentery with Sulfonamides, *J A M A* **123** 624-626 (Nov 6) 1943.

394 Yannet, H., Deutsch, J. V., and Lieberman, R. The Use of Sulfaguanidine for Prophylaxis in Sonne Dysentery and in the Control of the Carrier State, *Yale J Biol & Med* **16** 443-450, 1944.

395 Smith, H. G. Sulphaguanidine for Flexner Dysentery, *Brit M J* **1** 287-288, 1944.

reacted to a sensitization dose of other sulfonamide compounds, this fact suggests that the guanidine radical may be the sensitizing agent

Thirty carriers of *Shigella paradysenteriae* were treated with 20 Gm of sulfaguanidine for six days and 55 with 20 Gm of succinylsulfathiazole for six days³⁹⁶ Dysentery bacilli disappeared from the stools in every patient, the criterion being a minimum of nine consecutive negative reports after cessation of treatment No significant toxic reactions attended the use of either drug, but the patients receiving succinylsulfathiazole experienced minor annoyances Page³⁹⁷ reports on 208 cases of bacillary dysentery treated with sulfaguanidine with no deaths or serious complications, in 91 per cent *Shigella paradysenteriae* was found and in 8 per cent *Shigella sonnei* In 28 per cent of the cases, in all of which the disease was due to *S. paradysenteriae*, negative stools were not obtained after a ten day course with sulfaguanidine, these responded to a five day course of succinylsulfathiazole In a study of 200 cases of confirmed bacillary dysentery, sulfaguanidine gave results superior, both clinically and bacteriologically, to those from aperients and chalk, but, even so, 30 per cent of the patients still had bacteriologically positive stools in convalescence, as compared with 50 per cent with the other treatments³⁹⁸ Pyrexia did not appear to influence the effect of sulfaguanidine to any great extent The use of broth enrichment technic revealed many positive results which would have been missed if direct plating had been employed Baker³⁹⁹ treated 26 patients with sulfaguanidine and 31 patients with sodium sulfate The patients receiving sulfaguanidine had a more rapid reduction in the diarrhea, less toxemia and a quicker return of the rectal mucosa to normal on proctoscopic examination Chronic Flexner

dysentery treated successfully with succinylsulfathiazole is reported⁴⁰⁰

Poth and Ross⁴⁰¹ found that when N4-phthalylsulfathiazole is fed to dogs in doses of 0.25 Gm per kilogram of body weight per day the coliform organisms may be completely eliminated from the bowel in three days There was no evidence of toxicity The bacteriostatic effect is two to four times that of succinylsulfathiazole With this dosage the concentration of the drug in the blood did not exceed 3 mg per hundred cubic centimeters Callomon and Raiziss,⁴⁰² studying the bactericidal action of succinylsulfapyrazine and malylsulfathiazole against the intestinal coliform flora of normal mice, found the former to be more effective than succinylsulfathiazole and equal to sulfaguanidine, whereas the latter approximated succinylsulfathiazole in effectiveness Four new sulfonamide drugs — sulfamerazine, phthalylsulfadiazine, phthalylsulfamerazine and phthalylsulfathiazole — were tested in vitro by Schweinburg and Yetwin for their action against certain enteric pathogens⁴⁰³ On the whole, the action of these drugs was similar to that of the older sulfonamide compounds The shigellas proved more susceptible than other organisms

Boyd and Portnay⁴⁰⁴ found that bacteriophage of high specific potency was of no prophylactic or therapeutic value in treatment of bacillary dysentery

Cholera—Huang⁴⁰⁵ reports that only 1 of 22 patients with Asiatic cholera treated with sulfaguanidine died and that the patients showed general improvement from three to four hours after the beginning of treatment

400 Caldwell, W A, and Hardwick, S W Chronic Flexner Dysentery Treated with Succinylsulphathiazole, *Lancet* 2 544, 1943

401 Poth, E J, and Ross, C A Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives, *Texas Rep Biol & Med* 1 345-370, 1943

402 Callomon, F T, and Raiziss, G W Effect of Oral Administration of Succinyl Sulfapyrazine on Bacterial (Coliform) Flora of the Intestine of Normal Mice, *J Pharmacol & Exper Therap* 79 200-207, 1943

403 Schweinburg, F B, and Yetwin, I J In Vitro Action of Sulfamerazine, Phthalylsulfadiazine, Phthalylsulfamerazine and Phthalylsulfathiazole on Enteric Pathogens, *New England J Med* 230 510-514, 1944

404 Boyd, J S R, and Portnay, B Bacteriophage Therapy in Bacillary Dysentery, *Tr Roy Soc Trop Med & Hyg* 37 243-262, 1944

405 Huang, J S Treatment of Asiatic Cholera with Sulfaguanidine, *J A M A* 125 23-24 (May 6) 1944

396 Hoagland, R J Harris, F H, and Raile, R B Treatment of Bacillary Dysentery Carriers, *War Med* 4 400-403 (Oct) 1943

397 Page, S G, Jr Sulfaguanidine in the Treatment of Bacillary Dysentery, *Bull U S Army Med Dept*, 1944, no 72, pp 50-62

398 Jamieson, W M, Brodie, J, and Stiven, D Bacillary Dysentery in Dundee A Comparative Study of Treatments, *Brit M J* 1 322-324, 1944

399 Baker, B A The Therapeutic Value of Sulfaguanidine in the Treatment of Bacillary Dysentery at an Australian General Hospital, *M J Australia* 1 435-439, 1944

ALBRIGHT'S SYNDROME

(POLYOSTOTIC FIBROUS DYSPLASIA WITH CUTANEOUS PIGMENTATION IN BOTH SEXES AND GONADAL DYSFUNCTION IN FEMALES)

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The relationship of the parathyroid gland to calcium metabolism had been known for many years, but it was not realized until 1926 that widespread decalcification of the skeleton can be produced by a functioning parathyroid tumor. This discovery provided a wealth of new information relative to the abnormal metabolism of bone and also furnished the clue to successful treatment of hyperparathyroidism by surgical extirpation of the tumor. In certain cases, however, the clinical picture was not entirely typical of hyperparathyroidism.¹ The bony lesions developed in childhood and were spotty or disseminated rather than generalized² and sometimes were predominantly unilateral.³ Extraskelatal abnormalities, such as large areas of cutaneous pigmentation, were noted, and in females precocious puberty was an outstanding feature.⁴ Three seemingly dissociated manifestations, namely, disseminated fibrosis of bone, cutaneous pigmentation and precocious puberty among females, completed a syndrome which Albright and his co-workers⁵ described in 1937 and which since that time generally has been known as Albright's syndrome.

From the Division of Surgical Pathology (Dr Dockerty), the Section on Orthopedic Surgery (Dr Ghormley), the Section on Pediatrics (Dr Kennedy) and the Section on Roentgenology (Dr Pugh) of the Mayo Clinic

1 Meyerding, H W Cystic and Fibrocystic Disease of the Long Bones, *Am J Orthop Surg* **16** 253-276 (Sept), 367-382 (Oct) 1918

2 Freund, E, and Meffert, C B On the Different Forms of Non-Generalized Fibrous Osteodystrophy The Localized, the Diffuse Monostotic, the Unilateral and the Monomelic Form, *Surg, Gynec & Obst* **62** 541-561 (March) 1936

3 Moehlig, R C, and Schreiber, F Polyostotic Fibrous Dysplasia Report of a Case with Unilateral Involvement, *Am J Roentgenol* **44** 17-23 (July) 1940

4 Borak, J, and Doll, B Halbseitige Recklinghausensche Knochenkrankheit mit Pubertas praecox, *Wien klin Wchnschr* **47** 540-541 (April) 1934

In addition to furnishing clinical, roentgenologic and pathologic evidence which established this condition as a fairly definite entity, Albright stated it could be differentiated from hyperparathyroidism.⁶ Thus surgical exploration of the neck could be avoided. His theory of the causation of this disease, namely, that the manifestations arose as a result of a congenital developmental defect involving many types of tissue, is perhaps hypothetic, but it has not yet been superseded by anything more specific or enlightening.

Albright's original communication stimulated intense interest in the syndrome which now bears his name, and other investigators presented isolated cases they had observed personally and cited from the literature earlier cases which had been hidden under a veil of obscure terminology. Prominent among these investigators were Lichtenstein and Jaffe.⁷ Their attention was focused particularly on the associated lesions of bones, for which they coined the term polyostotic fibrous dysplasia. They attempted to show that in all cases studied the nucleus of the disorder seemed to center in the bony lesions, which when widespread were

5 Albright, F, Butler, A M, Hampton, A O, and Smith, P Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females Report of Five Cases, *New England J Med* **216** 727-746 (April 29) 1937

6 Albright, F, Scoville, B, and Sulkowitch, H W Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation, and a Gonadal Dysfunction Further Observations Including the Report of Two More Cases, *Endocrinology* **22** 411-421 (April) 1938

7 (a) Lichtenstein, L Polyostotic Fibrous Dysplasia, *Arch Surg* **36** 874-898 (May) 1938 (b) Lichtenstein, L, and Jaffe, H L Fibrous Dysplasia of Bone A Condition Affecting One, Several or Many Bones, the Graver Cases of Which May Present Abnormal Pigmentation of Skin, Premature Sexual Development, Hyperthyroidism or Still Other Extraskelatal Abnormalities, *Arch Path* **33** 777-816 (June) 1942

associated sometimes with one or more of the other manifestations of Albright's syndrome. At the present time many of the older terms, such as *osteitis fibrosa disseminata* and *focal osteitis fibrosa cystica*, have been replaced to some extent by the term Albright's syndrome or *polyostotic fibrous dysplasia*, or by both.

No useful purpose would be served by a further discussion of the historical events that led up to the newer conception of this disease. This material has been presented in many excellent articles which have appeared with increasing frequency since 1937. Two of the more recent and complete reviews were made by Neller⁸ in 1941 and by Gorham and co-workers⁹ in 1942. The last-named investigators tabulated data gleaned from recorded cases of Albright's syndrome as it appears in both its complete and its incomplete form. Our purpose in this paper is to add to their table the case of Shallard¹⁰ and 6 cases encountered at the Mayo Clinic (outlined in the table).

REPORT OF CASES

CASE 1—A white woman 35 years of age came to the clinic on Jan 12, 1943.¹¹ During March 1942, in the second trimester of her third pregnancy, she had sustained a pathologic fracture of the right femur. This apparently had healed under ordinary methods of treatment, but it was followed by a foot drop on the same side. This in addition to the gradual enlargement of a known pelvic tumor made the patient seek medical advice at the clinic.

The salient features in the patient's past history were as follows. At the time of birth she had weighed 4 pounds (1,815 Gm) and her twin brother 8 pounds (3,629 Gm). At birth she had large brown spots on the right cheek, neck and posterior cervicothoracic region, as well as on both buttocks and the left thigh. She stated that she had grown and matured rapidly, her height at 10 years of age exceeding that of her twin by an inch (25 cm). By the age of 14 she had attained her maximal height of only 4 feet, 11 inches (150 cm). Her twin had continued to grow steadily until the age of 17, at which time he was 6 feet (183 cm) in height. At the age of 7 years menstruation had begun, concomitant early enlargement of the breasts occurred. She had married at the age of 24 and subsequently had gone through three pregnancies

Physical examination at the clinic revealed a short woman who had a protuberance of the lower part of the abdomen, a foot drop on the right side and large, irregular, deeply pigmented areas of skin in the locations previously mentioned (fig 1). The right leg, in comparison with the left leg, was somewhat atrophied and was 2 inches (5 cm) shorter. The achilles reflex was absent on the right side, and the Babinski sign was positive bilaterally.

Roentgenograms of the skeleton revealed lesions that were interpreted as being typical of *osteitis fibrosa*. The locations of these lesions are shown in figure 2. The greatest involvement was in the right lower extremity. The right femur showed evidence of a healed pathologic fracture in its middle portion. The concentrations of serum calcium, phosphorus, phosphatase, cholesterol and so forth were well within the limits of normal, indicating that the bony lesions were prob-



Fig 1 (case 1)—Pigmented areas (a) on buttocks, left thigh and right cervicothoracic region and (b) on chin, right mandibular and anterior cervical regions. The abdominal distention is the result of the underlying pelvic tumor.

ably quiescent. The concentration of estrogen in the urine was normal.

At operation on January 14 a lateral incision below the trochanter of the right femur disclosed normal periosteum and a thinned cortex investing a central portion which was mottled red and grayish white and of a soft, cheesy consistency. Some of this tissue and a small portion of pigmented skin of the right buttock were removed for biopsy (fig 3), and the observations were similar to those described in the subsequent cases.

At operation on February 1, a large mucinous cystadenoma was removed from the left ovary. Biopsy of the right ovary was performed and showed normal ovarian cortex.

The patient made an uneventful convalescence from both operations and was dismissed after a regimen of

8 Neller, J. L. *Osteitis Fibrosa Cystica* (Albright), *Am J Dis Child* **61**: 590-605 (March) 1941.

9 Gorham, L. W., Campbell, E. H., Howard, W. P., Donhauser, J. L., and Rust, N. H. Albright's Syndrome. A Group of Cases Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and a Gonadal Dysfunction, *Clinics* **1**: 358-385 (Aug) 1942.

10 Shallard, B. T. *Osteitis Fibrosa Disseminata*, *M J Australia* **1**: 558-560 (April 20) 1940.

11 This is a summary of a case previously reported in detail (Dockerty, M. B., Meyerding, H. W., and Wallace, G. T. Albright's Syndrome [Fibrous Dysplasia of Bones with Cutaneous Pigmentation in Both Sexes and Gonadal Dysfunction in Females], *Proc Staff Meet, Mayo Clin* **19**: 81-88 [Feb 23] 1944).

A Tabulated Record of Thirty-Nine Cases of Albright's Syndrome in Its Complete Form

Case	Author	Date	Age, Years	Sex	Duration, Years	Precocious Puberty	Pigmented Outaneous Spots	Number of Fractures	Roentgenologic Diagnosis, O F C	Biopsy Diagnosis, O F C	Serum Calcium	Serum Phosphorus	Serum Phosphate	Exploration of Parathyroid Glands, No Tumor Found
1	Weil Klm Wehnschr 1 2114 2115 (Oct 14) 1922	1922	9	F	7½	+1½ yr	+	8	+	+	N			0
2	Hirsch 15	1929	30	M	22	0	+	Numerous	+	+	N			++
3	Priesel, R., and Wagner, R. Ztschr f Kinderh 53: 146-161 (April 11) 1932, their case 1	1932	13	M	2	0	+	0	+	+	N			+
4	Priesel, R., and Wagner, R. Ztschr f Kinderh 53: 146-161 (April 11) 1932, their case 2	1932	6¾	M	3 weeks	0	+	0	+	+	>			0
5	Gaupp V Monatschr f Kinderh 53: 312-322, 1932, her case 2	1932	9	F	7	+9 yr	+	Several	+	+	N			+
6	Stalman, A. Virchows Arch f path Anat 259: 96-126 (April) 1933, his case 3	1933	8	F	3	+9 mo	+	Several	+	+	N			0
7	Snapper and Pansel 13	1933	10	F	3	+7 yr	+	6	+	Xanthomatosis	N			++
8	Goldhamer, K. Fortschr a d Geb d Rontgen strahlen 49: 456-481 (May) 1934	1934	9	F	7	+2 yr	+	1	+	?	N			0
9	Hummel, R. Rontgenpraxis 6: 513-519 (Aug) 1934, his case 1	1934	11	M	5	0	+	Several	?	Juvenile Paget's				0
10	Hummel, R. Rontgenpraxis 6: 513-519 (Aug) 1934, his case 2	1934	9½	M	2	0	+	0	?	Juvenile Paget's				0
11	McCune and Bruch 17b	1937	9	F	7	+2 yr	+	Numerous	+	+	N			+
12	Albright and others, 5 their case 1	1937	23	F	15	+7 yr	+	8	+	+	N			0
13	Albright and others, 5 their case 2	1937	39	F	29	+1 yr	+	1	+	+	N			0
14	Albright and others, 5 their case 3	1937	3½	F	3	+4½ mo	+	0	+	+	N			0
15	Albright and others, 5 their case 4	1937	8	F	4½	+3½ yr	+	0	+	+	N			0
16	Albright and others, 5 their case 5	1937	10	M	6	0	+	3	+	+	N			++
17	Pagniez, P., Plehet, A., and Fauvet, J. Bull et mem Soc med d hop de Paris 54: 733-736 (May 9) 1938	1938	36	M	33	0	+	5	+	+	N			0
18	Albright, Scoville and Sulkowitch, 6 their case 1	1938	21	M	16	0	+	6	+	+	>			++
19	Albright, Scoville and Sulkowitch, 6 their case 2	1938	14	M	12	0	+	1	+	+	>			0
20	Musser, H. H., and Barnwell, R., in discussion on Albright, Scoville and Sulkowitch, 6 pp 420-421	1938	11	M	4	0	+	2	+	+	>			++
21	Braid, 10 her case 1	1939	11	M	9	0	+	Numerous	+	+	N			0
22	Braid, 10 her case 2	1939	3	F	1½	+2½ yr	+	4	+	+	N			0
23	Summerfeldt and Brown, 18 their case 1	1939	10	F	7	+3 yr	+	3	+	+	N			0
24	Summerfeldt and Brown, 18 their case 2	1939	6	F	4	+2 yr	+	0	+	+	N			0
25	Robson, K., and Todd, J. W. Lancet 1 377-380 (Feb 18) 1939	1939	33	F	27	+7 yr	+	Several	+	+	N			+
26	Mondor, H., and others J de chir 53: 593-624 (May) 1939	1939	14	F	7	+7 yr	+	Numerous	+	+	N			0
27	Diez J Prensa med argent 26: 1870-1897 (Sept 27) 1939	1939	18	F	7	+5 yr	+	Numerous	+	+	N			+
28	Nichols, 24	1940	31	M	24	0	+	Numerous	+	+	N			++
29	Shallard 10	1940	18	F	10	+4 yr	+	2	+	+	N			+
30	Neller 8	1941	7	M	1	0	+	3	+	+	N			++
31	Stauffer, H. M., Arbuckle, R. A., and Aegerter, L. J. Bone & Joint Surg 23: 333-334 (April) 1941	1941	10	M	16½	0	+	3	+	+	N			+
32	Thomson, H. W., Meredith, T. N., and Wunderly, H. L. J Pediatr 18: 638-642 (May) 1941	1941	13	M	10	0	+	3	+	+	N			0
33	Gorham and others 9	1942	14	M	6	0	+	2	+	+	N			0
34	Case 1†	1944	35	F	28	+	+	1	+	+	N			0
35	Case 2†	1944	6	F	4½	+	+	1	+	+	N			0
36	Case 3†	1944	14	F	8	+	+	1	+	+	N			0
37	Case 4†	1944	3	F	1	+	+	Multiple	+	+	N			0
38	Case 5†	1944	28	M	9	0	+	1	+	+	N			0
39	Case 6†	1944	10	M	3	0	+	1	+	+	N			0

* Part of this tabulation was compiled by Gorham and others

† Of this paper

List of Abbreviations

O F C, osteitis fibrosa cystica, N, normal, > greater than normal, <, less than normal, + present or done, 0, absent or not done, . not recorded, ? , doubt as to diagnosis

aluminum acetate had been started according to the method advised by Helfet¹²

Comment—This case is extremely interesting in that the patient had reached middle age before the bony disease manifested itself by the occurrence of the pathologic fracture of the right femur. Yet clinical and chemical studies one year later revealed that the pathologic process in the bones already had become quiescent. The onset of menses at the age of 7 years indicated premature sexual development. The fact that the patient grew faster than her twin brother but stopped growing at the age of 14, while he continued to grow until the age of 17, suggested

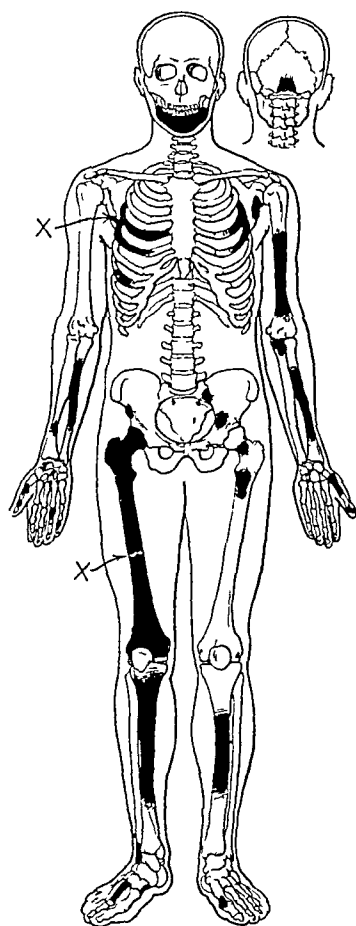


Fig 2 (case 1)—Zones of fibrocystic involvement of bones (black areas). Sites of pathologic fractures are indicated by "X"

precocious somatic development followed by premature arrest of growth. The pigmented areas of the skin were large and well defined. The presence of a large mucinous cystadenoma of the left ovary, which was apparently coincidental, also adds to the interest of this case.

CASE 2—A white girl 6 years of age was brought to the clinic on Aug 7, 1942, because of a broken left

leg. For three weeks she had been confined to her bed because the upper portion of the left leg had snapped under circumstances that suggested the presence of a pathologic process. Previous to this accident she had walked lamely on the left leg for two years.

The mother stated that the child had weighed 7 pounds (3,175 Gm) at birth, that the neonatal period had passed without incident and that early growth and development had been normal. She had walked at the age of 1 year and talked at 18 months and had just completed her first year of school. She had suffered from scarlet fever, whooping cough, measles and mumps between the ages of 1 and 5 years, but none of these childhood diseases had been associated with complications.

The patient had had three episodes of vaginal bleeding, which had occurred at the ages of 1½ years, 2½ years and 3 years. When she was about 3 years of age, her mother had noted enlargement of both the child's breasts and the appearance of fine suprapubic hairs.

Physical examination revealed a thin girl who was irritable and definitely precocious. The breasts were developed to the extent expected in a girl of 16 years. There was a fine growth of axillary and pubic hair. The left leg, which was encased in a Thomas splint, was swollen and tender in its upper portion. Any movement of the leg produced severe pain. A large area of cutaneous pigmentation was present on the inner aspect of the left thigh. A napkin designed to protect the perineum against traumatic irritation by the splint was blood stained. The blood was found to be vaginal in origin.

The results of laboratory examinations were essentially negative. The concentrations of serum calcium and serum phosphorus were within normal limits, and the value for serum phosphatase was 39 Bodansky units. Roentgenograms revealed cystic disease of the entire left femur, with a pathologic fracture through a region of osteitis fibrosa located just below the greater trochanter. Some degree of periosteal reaction was evident. Similar zones of osseous rarefaction were noted in the region of the trochanter of the right femur, the right ilium, the left fibula and the left acetabulum (fig 4). Roentgenograms of the skull, spinal column, left and right upper extremities and right lower extremity revealed no other abnormality except a bone age consonant with a chronologic age of 13 years.

Surgical exploration on August 13 revealed a pathologic fracture through a cystic cavity in the upper end of the left femur. The cavity, which was surrounded by a thin shell of cortical bone, was filled with blood clots and disorganized reddish gray tissue. Laboratory examination of some of this tissue ruled out the possibility of cancer. The existence of Albright's syndrome was suggested by the microscopic appearance of the fresh tissue, which was compatible with that of osteitis fibrosa. Accordingly the cavity was bridged by an autogenous bone graft removed from a healthy portion of the left tibia. The leg was immobilized by application of a cast.

Shortly after the operation the use of aluminum acetate was instituted, according to the method advised by Helfet, and this therapy was continued after the patient's dismissal. At the time of preparation of this report in August 1944, the parents had reported that the fracture had healed satisfactorily, but they had expressed concern over recurrence of the menstrual bleeding.

12 Helfet, A. J. A New Conception of Parathyroid Function and Its Clinical Application. A Preliminary Report on the Results of Treatment of Generalized Fibrocystic and Allied Bone Diseases and of Rheumatoid Arthritis by Aluminum Acetate, *Brit J Surg* 27: 651-677 (April) 1940.

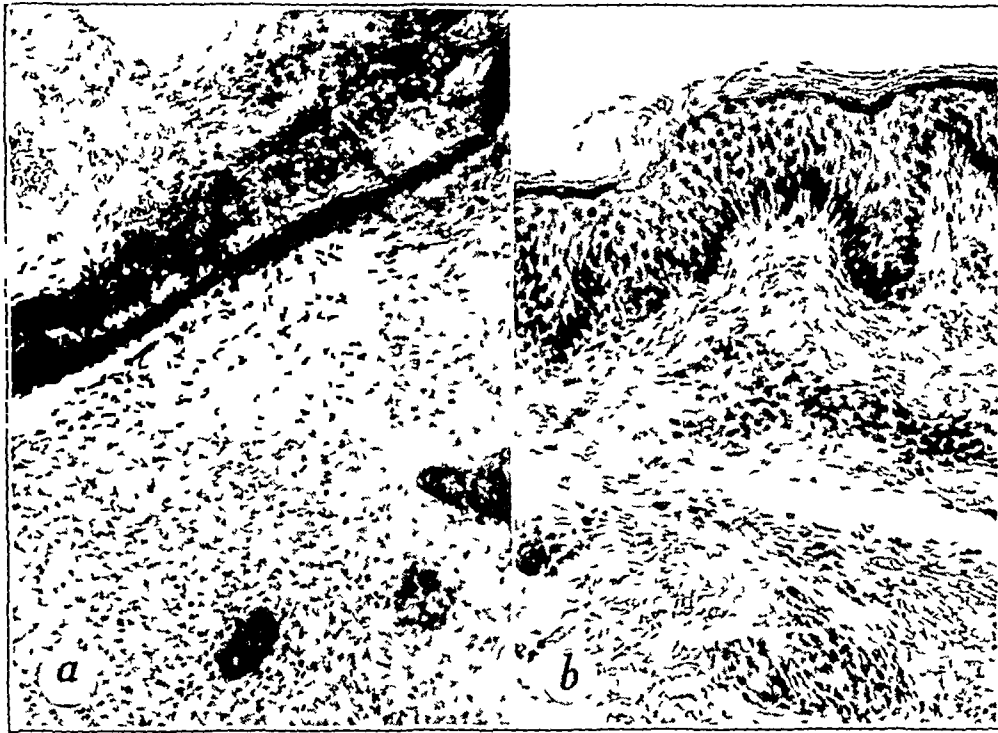


Fig 3 (case 1) —(a) Typical microscopic picture of bony lesions in Albright's syndrome showing extensive osteitis fibrosa with spicules of degenerating bone and no particular osteoclastic absorption ($\times 115$), (b) lesion from the skin of the buttock showing pronounced hyperpigmentation of the basal layers of the epidermis and no suggestion of formation of nevus ($\times 165$)

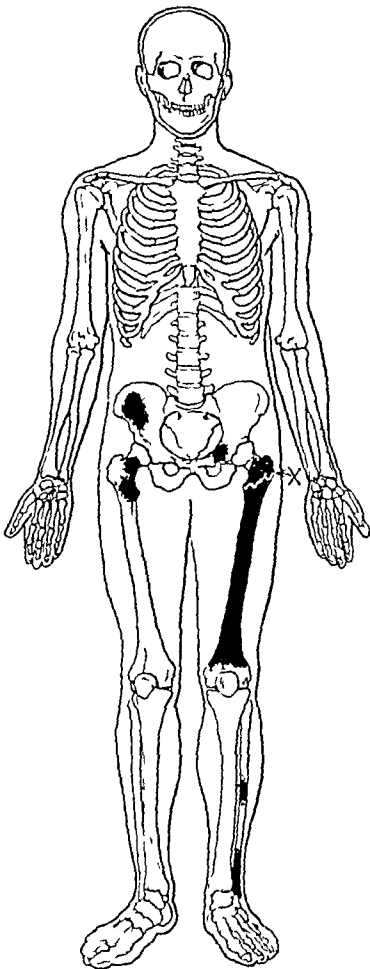


Fig 4 (case 2) —Zones of fibrocystic involvement of bones (black areas) Site of pathologic fracture is indicated by "X"

The pathologic tissue was reddish gray, obviously infiltrated with blood, friable and gritty to palpation. Microscopically the basic element appeared to be spindle-shaped fibroblasts loosely or compactly arranged in a picture resembling osteitis fibrosa (fig 5 a)

Three variations from this picture were noted 1 In some areas giant cells were present in such abundance that a diagnosis of benign giant cell tumor appeared warranted from a study of isolated fields (fig 5 b) Moreover, these giant cells contained as many as sixty to eighty nuclei and were indistinguishable from those encountered in typical giant cell tumor This feature is in contrast to that generally reported in the literature that is, that in polyostotic fibrous dysplasia giant cells are scanty or absent and when present demonstrate many atypical degenerated forms 2 In other areas microscopic spicules of degenerating bone which did not appear to be surrounded by osteoclasts were present Such an observation is in keeping with those of Jaffe 3 Hemorrhage, old and recent, was everywhere in evidence, and where infiltration (fig 5 c) of the tissues with hemosiderin was heaviest numerous foam cells appeared in small collections (fig 5 d) In the past such a picture has been interpreted to mean that the entire process is on the basis of caseous xanthomatosis¹³ However, focal accumulations of foam cells occasionally may be found in any lesion in which hemorrhage leads to destruction of tissue Their presence under these circumstances is on the basis of phagocytosis of lipid material liberated after the disintegration of cells, and the postulation of a generalized condition of lipodystrophy becomes unnecessary

13 Snapper, I, and Parisel, C Xanthomatosis Generalisata Ossium, *Quart J Med* 2 407-417 (July) 1933

14 Boenheim, C Frage der nervösen Komplikationen bei spezifischkindlichen Infektionskrankheiten und Vaccination, *Klin Wchnschr* 6 1552-1555 (Aug 13) 1927 Ford, F R, and Guild, H Precocious Puberty Following Measles Encephalomyelitis and Epidemic Encephalitis, with Discussion of Relation of Intracranial Tumors and Inflammatory Processes to Syndrome of Macrogenitosomia Praecox, *Bull Johns Hopkins Hosp* 60 192-203 (March) 1937

Comment—The salient clinical features in this case might be listed as the occurrence of precocious puberty and cutaneous pigmentation in association with osseous lesions which were not widespread. The impression one obtains from the literature is that the extraskeletal changes accompany only the most florid examples of polyostotic fibrous dysplasia. In this

clastic type and of focal accumulations of foam cells constituted unusual observations.

CASE 3—A white girl 14 years of age was brought to the clinic on Aug 3, 1911, complaining of a tumor of the right forearm that had been present for one year. One month previously a specimen of the growth had been removed for biopsy and had been thought to reveal giant cell sarcoma. Amputation had been advised, but

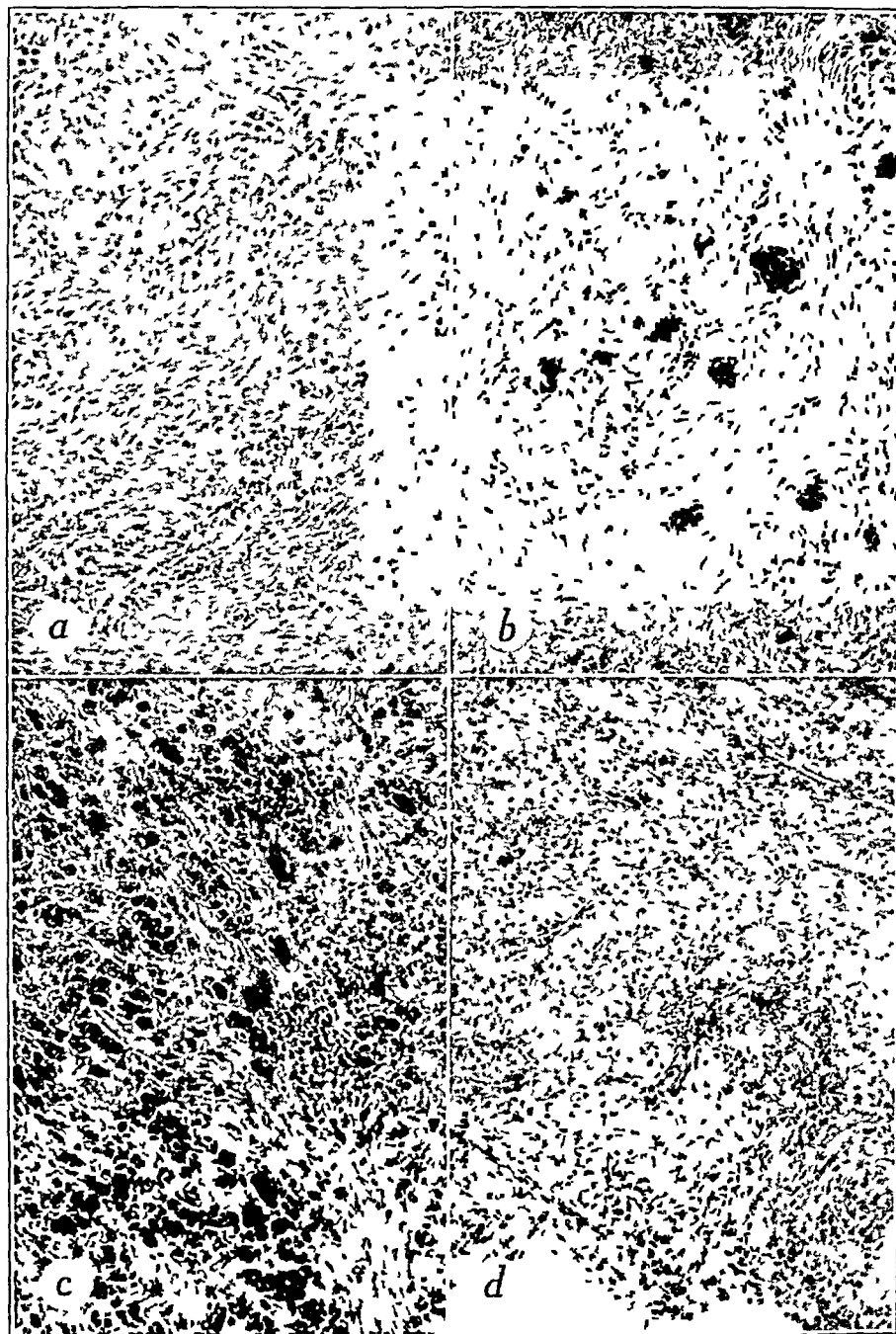


Fig 5 (case 2)—(a) Widespread replacement of bone with fibroblastic cells is apparent, the tissue is relatively avascular ($\times 180$). (b) Isolated zone presents a picture compatible with that of benign giant cell tumor of bone, the giant cells possess large numbers of nuclei, some blood pigment is present ($\times 110$). (c) Degenerating spicules of bone appear in a fibrous matrix impregnated with hemosiderin pigment ($\times 200$). (d) Isolated focus contains large numbers of foam cells, presence of these cells does not nullify a diagnosis of Albright's disease as was formerly thought ($\times 110$).

case almost the reverse was true. The unilateral character of the osseous lesions was in keeping with previously observed tendencies in Albright's syndrome. The presence on pathologic examination of typical giant cells of the osteo-

perimission was refused by the parents. Eight years prior to admission the patient had sustained a pathologic fracture of the right humerus. Resection of the upper 3 inches (7.6 cm) of the right radius was performed at the clinic on August 5 for a giant cell tumor. Convalescence was uneventful.

The patient returned in 1918, complaining of a tumor of the forehead and of another in the region of the right ankle. Both tumors had been painless and had grown slowly. The clinical record includes brief descriptions of semisolid osseous tumors in the locations mentioned and of a thoracic scoliosis. Roentgenograms of the two bony lesions were interpreted as revealing osteitis cystica of rather pronounced degree. At operation on February 14, the cystic degeneration was found to involve apparently the entire diaphysis of the right tibia. The cortex was thin and trabeculated. Contents consisted of fibrous degenerating material and some bone. It varied in density from soft cartilage to osseous material. In some regions it could be removed by curettage, and in others it was necessary to use the chisel. On examination the tissue removed presented the picture of osteitis fibrosa.

The third admission of this patient to the clinic occurred in 1928. She complained of swelling of the upper portion of the right arm of fifteen months' duration.

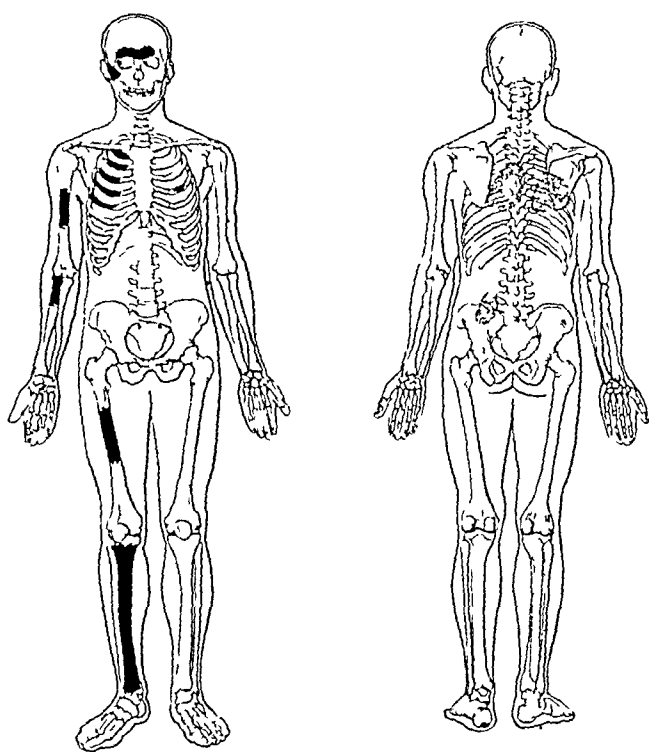


Fig 6 (case 3)—Zones of fibrocystic involvement of bones (black areas). Shaded areas show distribution of pigmentation.

The condition had come on rather suddenly and had been accompanied in the early stages by local pain and disability. The patient's history was reviewed carefully at this time and the following information was added to the clinical record. Menstruation, which had begun when the patient was 11 years of age, had been normal for about six months but always had been irregular thereafter. No pertinent data were noted regarding other evidences of precocious puberty. However, the patient's height of only 4 feet, 9 inches (144.7 cm) possibly represented precocious arrest of somatic development. In similar cases reported in the literature a short stature had been interpreted as being the end result of precocious changes in the bones. Four areas of cutaneous pigmentation were found on the patient's back. The largest of these, 3.2 inches (8 cm) in diameter, was located over the lower angle of the left scapula. The other three areas were located on the left buttock, over the middle portion of the right scapula and on the back of the left thigh. A moderate degree of thoracic

scoliosis was apparent. A tumor of osseous origin was located in the frontal region of the right humerus and another in the middle portion. There was no measurable shortening of any one of the four extremities, and the only limitation of motion observed was in the region of the operative scar around the right elbow joint.

Determinations of serum calcium revealed normal values. Roentgenographic studies of the bones of the extremities revealed lesions of the right humerus, right radius, right tibia and right femur which were interpreted as osteitis fibrosa. The lesion in the right humerus also showed evidence of an old incomplete fracture with some regional thickening of the bone in the area of clinical tumefaction. The right frontal region of the skull on roentgenographic study demonstrated changes similar to those present in the extremities.

Inasmuch as the bony lesions were causing no particular disability, operation was not urged, and the patient was sent home with instructions regarding a diet rich in minerals. She was advised to return if there was any adverse change in her condition.

The patient was last admitted to the clinic on Feb 14, 1940. She sought advice concerning a tumor in the breast, which proved at operation to be benign.

Clinically the orthopedic condition appeared to be quiescent. The values for serum calcium and serum phosphorus were within normal limits, but that for serum phosphatase was slightly increased (6.8 Bodansky units). Roentgenographic studies of the bones previously examined revealed little change from earlier observations, however, a thorough roentgenologic review revealed lesions in the right ilium and first, second, third, fourth and fifth ribs on the right (fig 6). A cystic area in the right zygomatic bone and increased density in the region of the frontal sinuses were noted. The only osseous lesion on the left side of the body was a small zone of rarefaction in the fourth rib. The patient was discharged without any special orthopedic treatment.

The pathologic material available for study consisted of the upper segment of the right radius and a few scrapings from the right tibia, both of which had been fixed for years in formaldehyde solution (10 per cent of the U S P concentration). On gross examination of the radial lesion, the cortex was found to be of eggshell thinness and was expanded in the form of a thin capsule over a brownish gray mass of tissue which replaced both marrow and substantia spongiosa in the upper third of the bone. This mass measured 9 by 7 by 6 cm and was of rubbery consistency but contained identifiable spicules of bone. It was solid throughout except for a small central zone of liquefactive softening. The lesion impinged on, but apparently did not invade, the epiphyseal end of the radius, which, with the capitulum, was intact and firmly fused with the diaphysis proximal to the previously mentioned region of softening (fig 7a). Microscopic sections made from the various parts of the lesion and stained routinely with hematoxylin and eosin revealed pictures comparable in many respects to those described in case 2. In many areas the picture was typical of benign giant cell tumor. In others the appearance recalled that of osteitis fibrosa cystica with a paucity of osteoclasts. Spicules of degenerating bone were observed lying in zones which demonstrated little by way of reactive absorption. In addition, many areas of young osteoid tissue were surrounded by a ring of osteoblasts (fig 7b). Several small islands of young cartilage were encountered (fig 7c), but only an occasional foam cell was found. Blood vessels were in general few, but evidence of previous hemorrhage in the form of scattered de-

posits of hemosiderin was everywhere apparent. Sections similarly prepared from the tibial lesion duplicated for the most part the microscopic patterns of sections prepared from the radial lesion (fig 7d). No cartilaginous elements were observed in any of the sections.

The salient clinical features in this case were the long evolution of the disease with periods of exacerbation and of remission covering a period of thirty years and the recent clinical quiescence of the lesions in spite of chemical activity as evidenced by the high level of serum phosphatase. Whether the onset of menses at the age of 11 years represented actual sexual precocity and whether an ultimate height of 4 feet, 9 inches (144.7 cm) actually indicated premature arrest of growth are questions that are perhaps somewhat equivocal.

CASE 4—A white girl 3 years of age was brought to the clinic on July 30, 1928, because of a lump on the right leg and difficulty in walking for one year. The family history was noncontributory. The patient was the younger of two children, her sister always had been perfectly well. The patient's birth and early development had been normal, but when she was about 12 months of age the parents had noted that the right leg was shorter than the left. At the age of 18 months, when the patient had begun to walk, a limp of the right leg was evident. Shortly thereafter the parents had noted a small lump in the middle portion of the right thigh. Since birth there had been an area of discoloration on the back of the head, and this area had always been devoid of hair. The child always had been bright mentally.

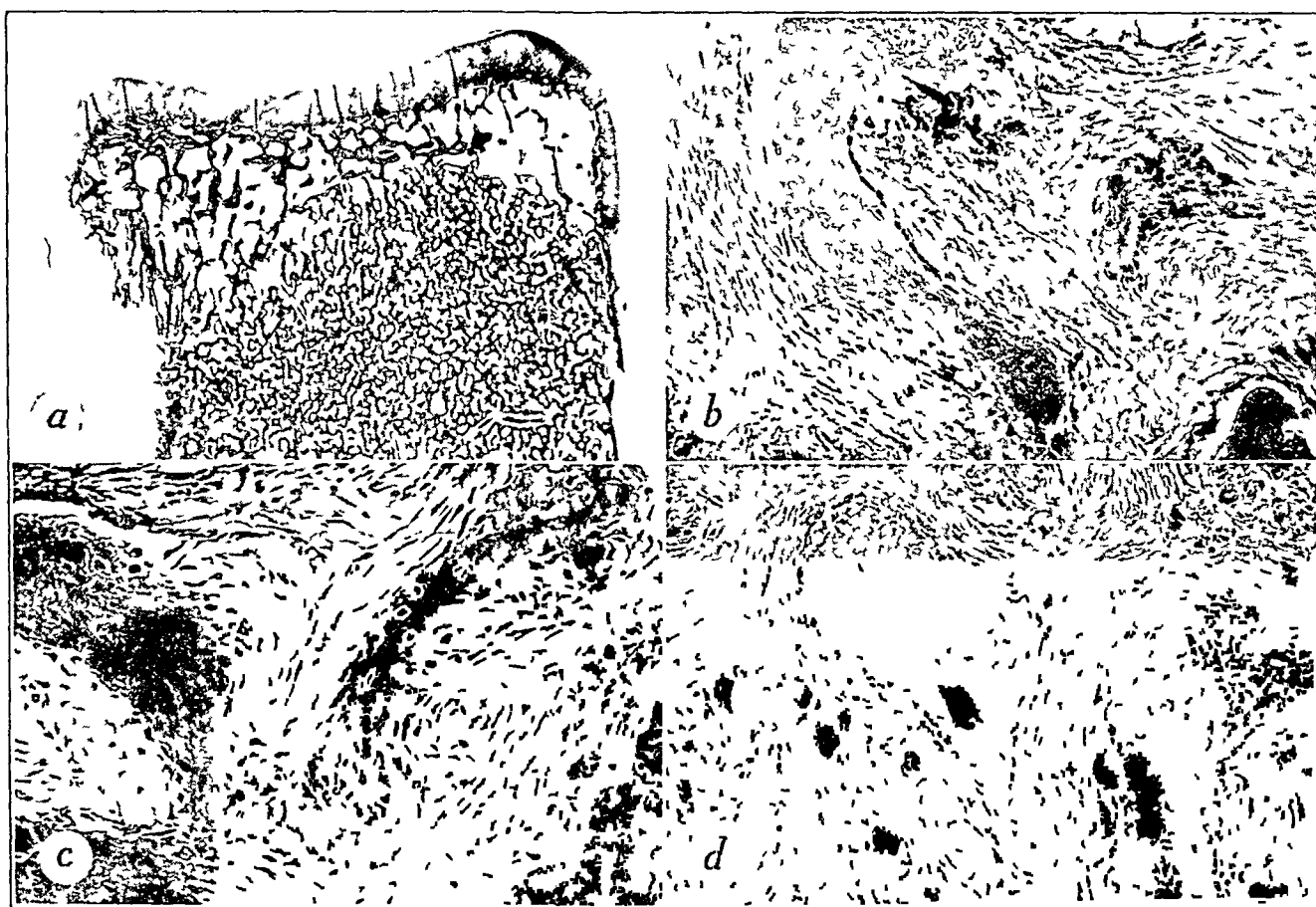


Fig 7 (case 3)—(a) Upper end of the resected radius proximal to the "brown tumor" (note the intact appearance of the radial epiphysis) ($\times 4$), (b) islands of osteoid tissue apparently surrounded by rings of dark-staining osteoclasts, some spicules of degenerating bone also present, osteoclastic activity minimal ($\times 100$), (c) an island of cartilage in a zone of osteitis fibrosa cystica ($\times 180$), (d) osteitis fibrosa of tibia with a fair number of giant cells ($\times 100$).

The osseous changes observed roentgenologically were almost exclusively on the right side, but the pigmented spots were located chiefly on the opposite side. This observation is recorded as being unusual, according to the literature on this bizarre disease.

Comment—This case is unusual from the pathologic standpoint in that a local so-called brown tumor of bone was diagnosed and treated in a fairly radical manner as a giant cell tumor. These tumors are of rare occurrence in the cases of Albright's syndrome recorded in the literature.^{7b}

Physical examination at the clinic revealed a well developed, well nourished child whose height was 3 feet, 2 inches (96.5 cm) and whose weight was 33 pounds (15 Kg). She walked with a limp that apparently resulted from the fact that the right leg was 1.6 inches (4 cm) shorter than the left. Some atrophy of the right leg was also present, and mild genu valgum was apparent. A moderate degree of left thoracolumbar scoliosis was interpreted as being compensatory in nature. Motions of the afflicted limb apparently were not limited, and no pain was elicited on pressure. A large area of alopecia was present on the occipital region of the scalp, and the skin overlying this area was pigmented. There was no evidence of

facial asymmetry, but asymmetry was noted in the region of the vulva, with apparent hypertrophy of the right labial folds. Examination of the thorax gave a negative result, except that a loud systolic murmur was heard over the entire precordial region. This murmur was transmitted to the left axilla and back and was not accompanied by a thrill, and it was thought to be attributable to a congenital cardiac defect that was not of a serious nature.

Results of laboratory examinations were essentially negative. Roentgenograms of the right lower and right upper extremities were interpreted as giving evidence of osteitis fibrosa, with the suggestion of a pathologic fracture involving the upper end of the right tibia. No osseous change in the ribs was noted in roentgenograms of the thorax.

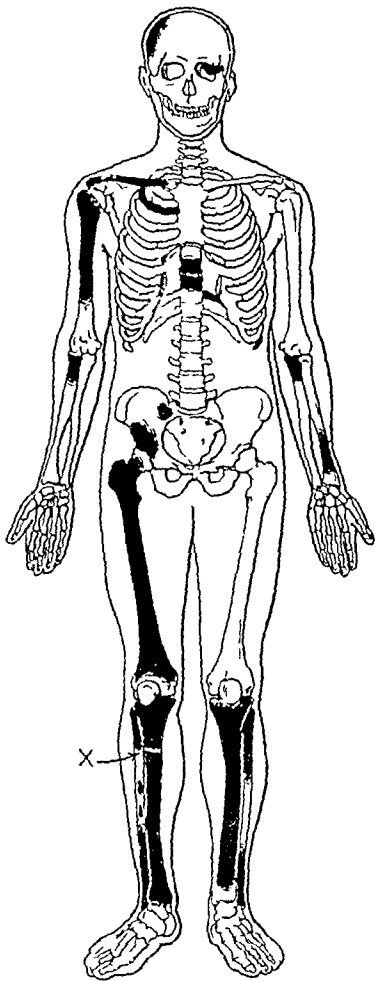


Fig 8 (case 4)—Zones of fibrocystic involvement of bones (black areas). Site of pathologic fracture is indicated by "X".

The consensus was that the patient was suffering from multiple congenital developmental defects. Since no specific treatment was known at that time, the parents were advised to bring her back periodically for reconsideration and for such symptomatic treatment as might be indicated by complications resulting from a possible progression of the osseous lesions.

From 1928 to 1932, the patient made yearly visits to the clinic. Roentgenologically the osseous lesions appeared progressive in extent and severity, although there was little clinical disability. Complete absence of typical symptoms seemed to rule out a diagnosis of parathyroid tumor. The possibility of xanthomatosis was considered, but a biopsy in 1932 of the osseous lesion of the right tibia demonstrated the picture of osteitis fibrosa without the presence of foam cells.

In 1934, a pathologic fracture was sustained through cystic lesions involving the lower ends of the right tibia and fibula. Fixation was accomplished by means of homogenous grafts. Roentgenograms made at the clinic were interpreted as revealing pronounced fibrocystic disease involving the femur, ilium, tibia and fibula on the right, both arms, right clavicle and acromion of the right scapula, ninth and tenth thoracic vertebrae, pelvis, right sacroiliac and acetabular regions, second right rib and eleventh left rib (figs 8 and 9). A considerable increase was noted in the extent of similar lesions of the skull in comparison with the degree of previous involvement (fig 9b). Some asymmetry was noted, the right parietal bone being thicker than the left. The value for serum calcium was 9.7 mg, for serum phosphorus 6.0 mg and for serum phosphatase 62 Bodansky units, per hundred cubic centimeters.

The patient returned to the clinic in 1941. She had sustained a pathologic fracture of the right femur in 1937. Several attempts to secure proper fixation by the method of open reduction had been unsuccessful. An attempt to add information to the clinical record also revealed that she began menstruating shortly after her twelfth birthday.

Small fragments of tissue preserved in formaldehyde solution (10 per cent of U S P concentration), which represented material removed from the tibia in 1932 and during the procedure of bone grafting in 1934, were available for study. Microscopic sections of both specimens stained with hematoxylin and eosin demonstrated the presence of osteitis fibrosa with a variable number of giant cells (fig 10a) and complete absence of foam cells. Some cartilage was present (fig 10b). In both specimens fragments of degenerating bone were present, as well as islands of osteoid tissue surrounded by zones of reactive osteoblasts. Considerable evidence of recent hemorrhage was evident in the tissue removed in 1934 from the site of the fracture but was absent in the specimen obtained for biopsy in 1932.

Comment—In this case the history is of "bone trouble" that was slow in evolution, beginning in childhood and continuing through adolescence with exacerbations and remissions. It was accompanied by the occurrence of a peculiar area of pigmentation of the scalp associated with localized alopecia. The fact that the patient's height measured 3 feet, 2 inches (97 cm) at the age of 3 years, 4 feet (122 cm) at the age of 6 and only 4 feet, 5 inches (135 cm) at the age of 15 might well indicate that an early acceleration of growth perhaps had been arrested prematurely. This observation is in accord with the observed phenomena of Albright's syndrome. Precocity completed the bizarre clinical picture, but this precocity, except for the labial hypertrophy, was characterized by early somatic rather than early sexual development. The observed value for serum phosphatase was probably lower than that expected, considering the extent and activity of the osseous lesions. The delayed union in the healing of the femoral fracture was perhaps unusual. Roentgenographic highlights consisted of the development of new lesions with a predilection for bones on

the right side, an increase in severity and extent of older lesions with maximal changes in the lower extremities, thickening of bones of the cranial vault and sparing of bony epiphyses

CASE 5—A white man 28 years of age was admitted to the clinic on July 6, 1937, complaining of a porous condition of his bones. The family history was not significant. Childhood diseases included measles, mumps, whooping cough and chickenpox, none of which was described as being particularly severe. He had had

after a period of two months. The patient stated that he had cracked his ribs on many occasions, the first of these incidents occurring when he was 14 years of age. No positive information was elicited concerning the date of the onset of puberty.

Physical examination revealed a deformed, short man whose height was slightly more than 5 feet (152 cm) and whose weight was 126 pounds (57 Kg). Considerable outward bowing of the upper portion of the left arm was apparent. The left arm was 24 inches (6 cm) shorter than the right. There were also well defined thoracic kyphosis and lumbar scoliosis. The



Fig 9 (case 4)—Lesions of disseminated osteitis fibrosa involving (a) right femur and right ilium, (b) right parietal and left temporal regions of skull, (c) and (d) right tibia and right fibula with two pathologic fractures of tibia, (e) right upper extremity and (f) left radius and ulna. Lesions are characteristically spotty in distribution and predominantly unilateral and demonstrate a notable sparing of epiphyses. For complete picture of skeletal lesions see figure 8.

influenza in 1928 and gonorrhea in 1930. In 1929 the patient sustained a fracture of the left humerus when he attempted to lift a roll of rubber down from a shelf. Roentgenograms at that time revealed a cystic condition involving several bones. The fracture apparently healed. One year later the patient slipped and fell, again fracturing the left humerus. A third fracture of the same bone occurred in 1935 under circumstances which indicated the presence of a pathologic process. A cast was applied, and union was secured

patient had a barrel chest, and even when he assumed the standing position the lower ribs almost overrode the crests of the ilium. Two large areas of cutaneous pigmentation were noted over the region of the sacrum, one on each side. In addition, numerous freckles were scattered over the body. The external genitalia were normal except for the presence of varicocele on the left side. An enlarged thyroid gland constituted the only other important observation on clinical examination, which included a neurologic investigation.

Erythrocytes numbered 5,160,000 and leukocytes 7,400 for each cubic millimeter of blood. The value for hemoglobin was 15.3 Gm per hundred cubic centimeters of blood. Urinalysis and the flocculation test revealed nothing abnormal. The value for serum calcium was 9.6 mg per hundred cubic centimeters and for serum

Roentgenograms, interpreted as showing the picture of osteitis fibrosa, showed lesions in the following locations: sternum, left scapula, third, fourth, fifth, sixth and seventh ribs on the left and seventh rib on the right (fig 11), first metacarpus and entire radius on the left (fig 12a), left humerus (fig 12b), and eighth

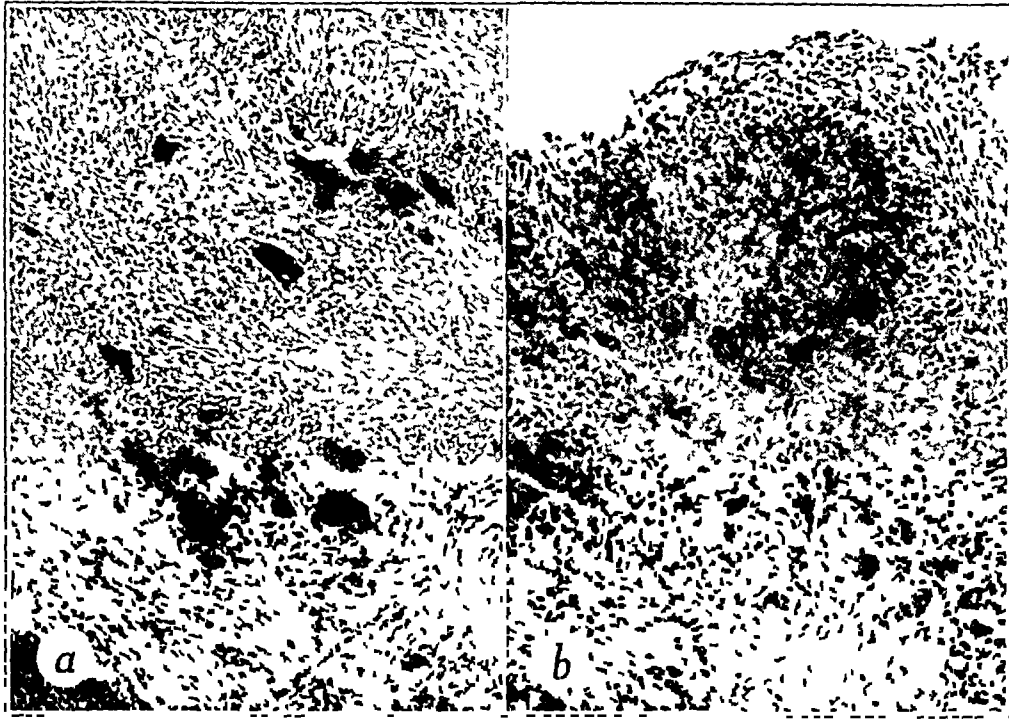


Fig 10 (case 4)—(a) Osteitis fibrosa of tibia with a sufficient number of giant cells in certain areas to warrant a diagnosis of giant cell tumor ($\times 80$), (b) islands of cartilage, as here depicted almost as diagnostic of Albright's syndrome as osteitis fibrosa itself ($\times 100$)

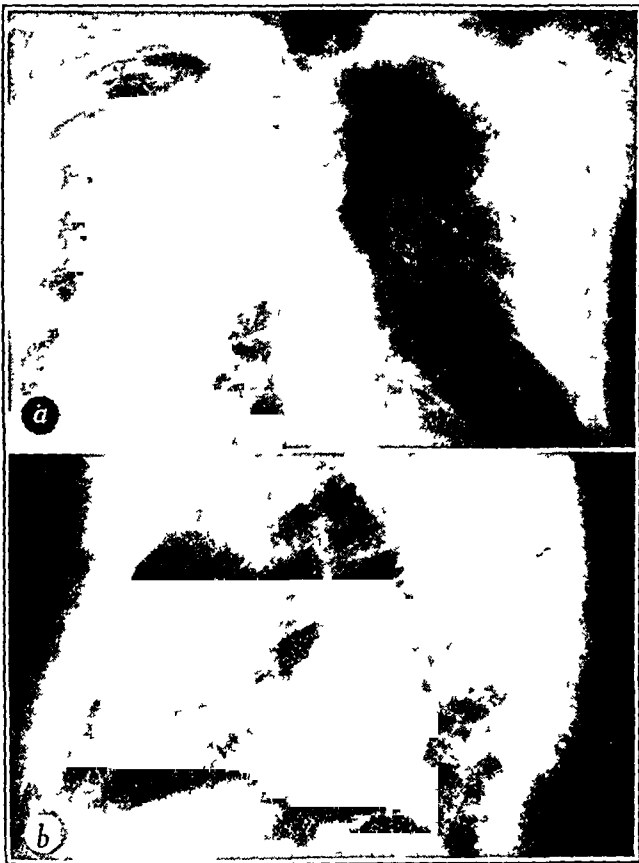


Fig 11 (case 5)—Lesions of osteitis fibrosa involving (a) ribs and scapula on left and (b) middle portion of sternum with expansile type of lesion

phosphorus 3.4 mg per hundred cubic centimeters, and the activity of serum phosphatase was equivalent to 10.4 Bodansky units



Fig 12 (case 5)—Lesions of osteitis fibrosa involving (a) first metacarpal bone and entire radius on the left and (b) entire left humerus. Zones of involvement predominantly left-sided. Complete skeletal involvement shown in figure 13

and ninth thoracic vertebrae with compression fractures and destruction of the pedicles. There were similar cystic changes in the second lumbar vertebra and in the wing of the sacrum on the right side (fig 13). What appeared at first to be a calculus in the left kidney proved on further investigation to be a large cystic defect involving the posterior portion of the twelfth rib on the left. Because the lesions were predominantly unilateral, the roentgenologists suggested that they were probably not the result of hyperparathyroidism. The bones, other than those previously

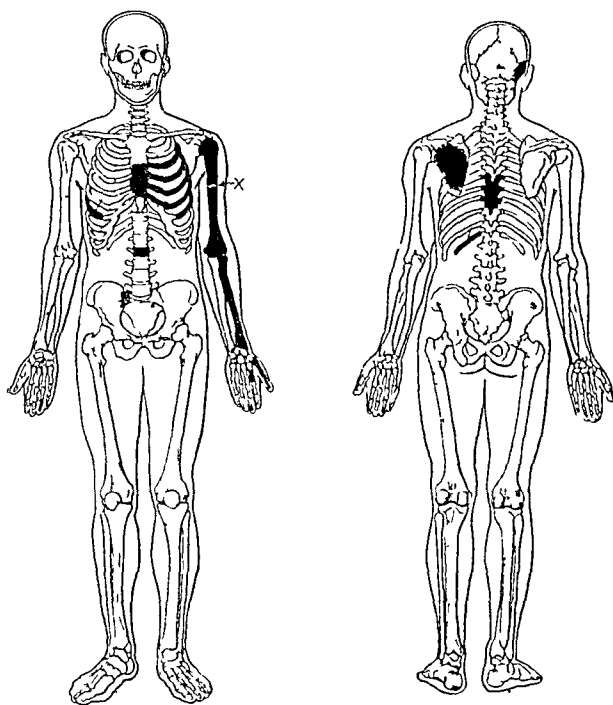


Fig 13 (case 5)—Zones of fibrocystic involvement of bones (black areas). Posterior view shows scapular and vertebral lesions. Site of pathologic fracture is indicated by "X".

mentioned, were roentgenoscopically normal. They suggested a diagnosis of polyostotic fibrocystic disease but were unable to rule out the possibility of myeloma.

On exploration of the left humerus on July 7, a small cyst was encountered after a thin shell of cortical bone was unroofed. A thick yellowish membrane was in apposition with the bone and surrounded a cavity filled with serous fluid. The medullary cavity was greatly expanded. Microscopic examination of a piece of the wall of the cyst and bacteriologic studies of some of the fluid revealed nothing of significance. On July 16 a small specimen was removed for biopsy from one of the pigmented areas over the sacral region. The patient was dismissed on the same day. When he was last heard from in 1941, he was still having trouble with recurrent fractures.

The pathologic material in this case consisted of a few small fragments of tissue from the capsule of the humeral cyst and tissue removed for biopsy from the skin in the area of pigmentation. Both specimens had been fixed in formaldehyde solutions (10 per cent of the U S P concentration). Sections prepared from the wall of the cyst revealed the picture of osteitis fibrosa with masses of fibroblastic cells loosely or compactly arranged in a rather avascular tissue. There were a few spicules of degenerating bone but practically no osteoid tissue. Giant cells were few

and widely dispersed, and foam cells were absent. Numerous red blood cells were present, and the tissue was impregnated with granules of hemosiderin. Sections made from the cutaneous lesion microscopically resembled those described in the literature on Albright's syndrome and presented the appearance of pronounced hyperpigmentation of the basal layers of the stratum granulosum (fig 14). There were no nevus cells or evidences of neurofibromas within the dermis.

Comment—In this case of Albright's syndrome occurring in a male, progressive lesions of the bones developed relatively late, were predominantly on the left side and involved chiefly the upper portions of the skeleton. A somewhat short stature naturally raised the question of possible precocious development with early arrest of somatic growth. The presence of the pigmented spots completed the syndrome.



Fig 14 (case 5)—Section of skin from pigmented area. The features of hyperpigmentation of the basal layers duplicate that illustrated in figure 3b ($\times 165$).

CASE 6—A white boy 10 years of age was brought to the clinic on Feb 13, 1941, for consideration of "bone trouble" which had been present for three years.

The family history was not significant, and early development had been normal. No sequelae had resulted from such childhood diseases as whooping cough, measles and chickenpox. When the patient was 7 years of age, the parents noted that he walked with a limp in the left leg. Medical advice was sought, and a diet rich in vitamins and minerals was recommended. Roentgenograms at that time were interpreted as revealing polyostotic fibrous dysplasia, a diagnosis which was confirmed by biopsy of a fragment of bone from the left hip and of a lesion involving one of the ribs on the right side. The values for serum calcium, phosphorus and phosphatase were approximately normal. Clinically and roentgenologically the condition seemed to progress rather than to improve. By May 1939, the patient was forced to use crutches, and later a brace became necessary. In September 1939, a fracture through the upper portion of the right femur was

sustained, but this healed as a result of immobilization of the leg in a cast. For eighteen months progressive deformity involving the left hip in the region of the fracture had been noticed.

Physical examination at the clinic revealed a somewhat undernourished child of about the stated age. His height was 4 feet, 8 inches (142 cm), and his weight was 67 pounds (30 Kg). There was a bulging deformity of the left leg over the region of the greater trochanter, with *coxa vara*. The left leg was 15 inches (38 cm) shorter than the right. No tenderness or limitation of motion was apparent. The only other significant physical feature was the presence of several large areas of pigmentation on the patient's back.

The values for serum calcium and serum phosphorus were, respectively, 10.1 and 3.6 mg per hundred cubic centimeters, and the activity of the serum phosphatase

much to be desired. However, the history was that of osseous lesions beginning in childhood, progressive in nature and complicated by the occurrence of a pathologic fracture. The fracture was demonstrated roentgenologically to have occurred through a fibrocystic portion. Pathologic verification of osteitis fibrosa had been obtained not only from the left femoral lesion but also from a similar lesion of a rib on the opposite side of the body. In view of the rather limited extent of the fibrocystic disease and the extensive cutaneous pigmentation, this case possibly represents another rather unusual example of Albright's syndrome.

ETIOLOGY

Although the cause of Albright's syndrome is a mystery, many investigators believe that the condition is the result of complex congenital errors in development.

Albright, impressed by the widespread distribution of lesions involving simultaneously the skin, bones and endocrine glands, postulated a primary disturbance of the central nervous system, possibly in the region of the hypothalamus. On this basis the endocrine manifestations were interpreted as arising from a disturbance of afferent impulses traveling to the pituitary body. The presence of mental disturbances in 1 of Albright's original cases served to strengthen his conviction concerning this hypothesis. Other positive neurologic signs have been recorded in several cases in the literature, and in case 1 of our series the presence of a positive Babinski sign bilaterally might support this hypothesis of a primary disturbance of the central nervous system. Even the sexual changes might occur as a result of lesions involving the central nervous system, as evidenced by the fact that these changes may follow encephalitis, poliomyelitis and even glioma, especially when the tumor is located in the region of the third ventricle and the hypothalamus. While it is perhaps noteworthy that in several cases of Albright's syndrome reported in the literature the patients had previously had encephalitis,¹¹ the evidence is by no means conclusive that encephalitis plays an etiologic role in the production of a disease considered by some investigators as beginning at, or even before, birth.

Possible evidence for a hereditary basis was presented in a case of polyostotic fibrous dysplasia studied by Moehlig and Schrieber. On the maternal side of the patient's family, shortness of stature and unusually early dental decay were interpreted as attributable to a hereditary defect in the bone-forming mesenchyma. Even if we could agree with this premise, we could

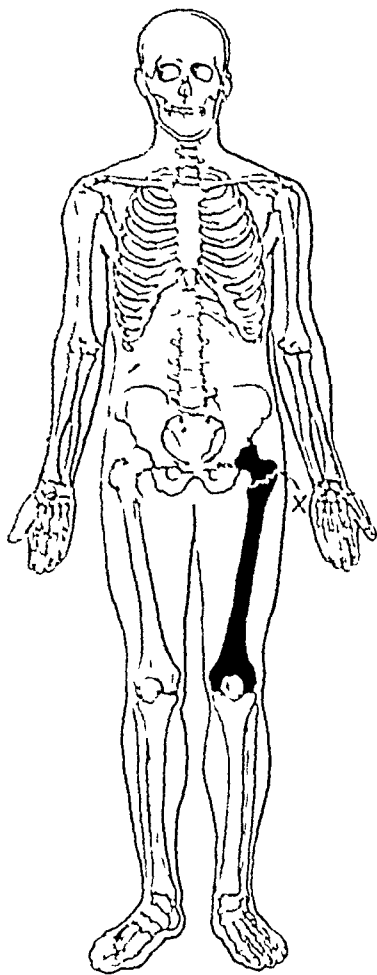


Fig. 15 (case 6)—Zones of fibrocystic involvement of bones (black areas). Site of pathologic fracture is indicated by "X".

was recorded as of 6 Bodansky units. Roentgenologic examination, limited by request to the left femoral lesions, revealed fibrocystic disease involving the entire shaft (fig. 15), an old intertrochanteric fracture and pronounced *coxa vara*.

Inasmuch as this patient was brought to the clinic solely for confirmation of the previous diagnosis of polyostotic fibrous dysplasia and for advice regarding the advisability of bone graft, a complete work-up was impossible. It was the consensus that a heterogenous graft carried across the zone of fracture would correct the deformity and effect a strong bony union.

Comment—Admittedly, from the standpoint of material available for study, this case leaves

not understand how, as they suggested, the unilateral distribution of the osseous lesions of their patient represented a chromosomal aberration for which the maternal side of the family could be blamed. In a search of the literature the only other evidence for a familial trait in polyostotic fibrous dysplasia appeared in a report by Hirsch¹⁵ of 3 siblings who all suffered from the effects of disseminated cystic lesions of bone.

In 2 cases of Albright's syndrome recorded by Braid,¹⁶ a history of neonatal jaundice suggested that disturbances in hepatic function were responsible for the syndrome. Braid obtained definite evidence, based on laboratory data, of diminished liver function in 1 of her cases. She correlated an increase in the value for serum phosphatase with an inability on the part of the liver to destroy this substance, noting that in certain cases of hepatic cirrhosis similar high levels of serum phosphatase are obtained. The cases of McCune and Bruch¹⁷ and of Summerfeldt and Brown¹⁸ were similar in many respects to those of Braid, and it is perhaps significant that 1 of our patients (case 3) stated that she "almost died of liver trouble in infancy." At necropsy in the case of McCune and Bruch the liver was found to have a normal microscopic appearance. Consequently a primary hepatic lesion probably could not be held responsible for the bony lesions of Albright's disease, to say nothing of the apparently unrelated sexual disturbances and the cutaneous pigmentation.

A primary hormonal imbalance has been postulated on the basis of those cases in which sexual aberrations were especially prominent. However, it is difficult, as Albright remarked, to comprehend how estrogen acting independently or through the medium of the parathyroid glands¹⁹ could explain the bizarre character and predominantly unilateral distribution of the

osseous and cutaneous lesions seen in this disease. Both estrogen and parathyroid extract have produced cystic changes of bone in animals,¹⁹ but none of these experiments has resulted in effects which combine the dissociated phenomena of Albright's syndrome.

Helfet, in an attempt to establish the nature of the osseous lesions, revived a theory that is interesting not only from the standpoint of etiology but also as a basis for therapy. He believed that there existed in Albright's syndrome a state of chronic hyperparathyroidism based on a mild hyperphosphatemia. His treatment consisted of reducing the amount of available phosphorus by precipitating part of it in the intestine by using the acetates and gluconates of aluminum. He reported some striking results after using this type of therapy for several patients who had polyostotic fibrous dysplasia of bone.

Sternberg and Joseph,²⁰ in one of the more recent reviews, presented some interesting etiologic data on the only case of Albright's syndrome in which complete necropsy had been performed. In this case, which previously had been studied and reported by McCune and Bruch, the patient, a 13 year old girl, subsequently had come under the care of Sternberg and Joseph for an attack of bronchopneumonia, which terminated fatally. The essential positive observations other than the osseous lesions, which are described in some detail, were limited for the most part to the endocrine glands, in which the following changes were noted. The pituitary body demonstrated pronounced hyperplasia of the basophilic elements with adenomas of microscopic size. The individual basophilic cells were larger than normal and decidedly pleomorphic. Binucleated and trinucleated giant forms were observed, with loss of granular structure. Colloid granular cytoplasm, present in certain of the cells, gave an appearance strikingly similar to "Crooke's change."²¹ The picture was interpreted as evidence of greatly disturbed function. The thyroid gland presented the microscopic picture of pronounced hyperplasia but contained numerous fetal adenomas, which Sternberg and Joseph interpreted as localized involution in a chronically toxic gland. This pa-

15 Hirsch, S. Is Generalized Osteitis Fibrosa (Paget and von Recklinghausen) Congenital? *Am J Surg* **3** 167-175 (Aug.) 1927.

16 Braid, F. Osseous Dystrophy Following Icterus Gravis Neonatorum. Generalized Osteitis Fibrosa with Areas of Pigmentation of the Skin and Precocious Puberty in the Female, *Arch Dis Childhood* **14** 181-202 (Sept.) 1939.

17 (a) McCune, D. J. Osteitis Fibrosa Cystica. The Case of a Nine Year Old Girl Who Also Exhibits Precocious Puberty, Multiple Pigmentation of the Skin and Hyperthyroidism, *Am J Dis Child* **52** 743-747 (Sept.) 1936. (b) McCune, D. J., and Bruch, H. Osteodystrophia Fibrosa. Report of a Case in Which the Condition Was Combined with Precocious Puberty, Pathologic Pigmentation of the Skin and Hyperthyroidism, with a Review of the Literature, *ibid* **54** 806-848 (Oct.) 1937.

18 Summerfeldt, P., and Brown, A. Osteodystrophia Fibrosa, *Am J Dis Child* **57** 90-101 (Jan.) 1939.

19 Bremer, J. L. Osteitis Fibrosa Localisata. An Experimental Study, *Arch Path* **32** 200-210 (Aug.) 1941.

20 Sternberg, W. H., and Joseph, V. Osteodystrophia Fibrosa Combined with Precocious Puberty and Exophthalmic Goiter. Pathologic Report of a Case, *Am J Dis Child* **63** 748-783 (April) 1942.

21 Crooke, A. C. A Change in the Basophil Cells of the Pituitary Gland Common to Conditions Which Exhibit the Syndrome Attributed to Basophil Adenoma, *J Path & Bact* **61** 339-349 (Sept.) 1935.

tient had a long history of toxic diffuse (exophthalmic) goiter, and the basal metabolic rate had ranged up to plus 120 per cent. The thymus and the lymph nodes showed considerable hyperplasia. Atrophy of the adrenal cortex contrasted with relative hypertrophy of the medullary tissue. Ovarian tissue resembled that of an adult woman, with multiple follicular cysts but with an absence of mature or maturing corpora lutea. Sternberg and Joseph contrasted this observation with the condition present in cases of adrenal cortical hyperplasia and tumor, in which the ovaries are often hyperplastic. Parathyroid glands were all identified and were essentially normal in appearance. Of particular interest was the authors' observation that the liver was normal in spite of the history of severe neonatal jaundice. It is perhaps also noteworthy that no lesions of the brain except a slightly dilated third ventricle, were demonstrated on either macroscopic or microscopic examinations and that no abnormality was evident on careful study of the hypothalamus.

Sternberg and Joseph found it impossible to accept the theory of causation based on the principle of multiple congenital defects of development even though, in addition to the manifestations of Albright's syndrome in its most florid form, their patient had had a patent foramen ovale and Meckel's diverticulum. It was their considered opinion that the osseous changes, cutaneous pigmentation and precocious puberty were on an endocrine basis and that in their case the etiologic importance of thyrotoxicosis was paramount. In the bizarre distribution of the osseous and cutaneous lesions they saw a "localized tissue susceptibility" paralleled by recorded instances of hemihypertrophy, hemiobesity, unilateral exophthalmos and so forth.

Several other cases of Albright's syndrome have been recorded in which clinical evidence of thyrotoxicosis was manifest, but in 1 of these biopsy of the thyroid gland revealed normal colloid thyroid. Moreover, the large majority of patients in the recorded cases did not have hyperthyroidism. Consequently the case of Sternberg and Joseph may fall into a special category. The changes they depicted as involving the basophilic elements in the pituitary body were as arresting as those in the thyroid gland, and perhaps some investigators would be inclined to feel that the endocrine manifestations had occurred as a result of a primary disorder involving the pituitary gland.

SYMPTOMS AND SIGNS

Next to the symptoms of precocious puberty in females, the osseous lesions that characterize Albright's syndrome provide the cardinal clinical

symptoms. Limitation of movement that results from bony deformity and pathologic fractures are often childhood manifestations. However, in cases 1 and 5 of our series extensive bony lesions had been practically unnoticed until the patients were well on in adult life. Generalized "bone pains," so characteristic of hyperparathyroidism, are usually absent in uncomplicated cases, but local pain and tenderness may be present if the involved bone is the site of an expanding fibrous tumor and are naturally present when a pathologic fracture has occurred. Strangely enough, these fractures tend to heal after the use of standard methods of immobilization or surgical fixation by means of grafts²² or both.

Lichtenstein and Jaffe were of the opinion that the osseous lesions constitute the nucleus of the disorder and felt that other clinical manifestations, such as precocious puberty and cutaneous pigmentation, can occur only in the presence of extensive skeletal involvement. Cases 2, 5 and 6 of our series provided notable exceptions to this general rule. Although precocious puberty is a cardinal symptom of Albright's syndrome in the complete form, it is almost exclusively limited to females and usually to those females in whom extensive osseous lesions are also present. However, there are exceptions to this rule, of which case 1 is an example. The reason for precocious puberty is poorly understood, but its implications are often far reaching, for in addition to the early onset of menstruation and the early appearance of secondary sexual characteristics there is sometimes pronounced acceleration in somatic maturation. Thus the bone age may exceed the chronologic age of the patient, in that there is premature ripening of the epiphyses. In addition, epiphyses unite early with diaphyses, and, in the case of bones of the extremities, the result may be a premature arrest of growth. It has accordingly been observed that adult females who suffer from the disease are of short stature.

INCIDENCE

Albright's syndrome is somewhat rare if one considers only the complete form, as exemplified by the cases listed in table 1 and, in addition, the occasional case which may have escaped our notice in a review of the literature. However, other authors, such as Gorham and co-workers, consider the incomplete form, in which one or more of the clinical, roentgenologic and pathologic features are lacking, and thus remove the condition somewhat further from the realm of

²² Ghormley, R. K., Sutherland, C. G., and Pollock, G. A. Pathologic Fractures, *J. A. M. A.* **109**: 2111-2115 (Dec. 25) 1937.

the uncommon. Furthermore, if one agrees with Lichtenstein and Jaffe that polyostotic fibrous dysplasia in its most florid expression demonstrates the extraskeletal manifestations of Albright's syndrome, an extensive literature is available. Jaffe, to cite one investigator, has had personal experience with at least 23 cases, and Albright has encountered approximately 30.

In the matter of sex, females predominate over males in the ratio of 3 to 2. It is interesting to note that this same ratio obtains for the sex incidence among patients suffering from the effects of parathyroid adenoma. No racial susceptibility to the disease has been emphasized in the literature.

It has been suggested in the literature that increased fertility may be a feature of Albright's syndrome in females. Moreover, it has been asserted that in the case of Lena Medina, the 5 year old Peruvian girl who gave birth to a boy, precocious puberty was attributable to this condition. However, a letter which one of us (M. B. D.) received from Albright,²³ who had corresponded with one of the physicians in charge of the case, did not confirm this theory.

Extensive cutaneous pigmentation, often occurring in the form of large irregular patches, is an almost constant accompaniment of osseous lesions of pronounced degree in Albright's syndrome. Strangely, these patches of pigmentation may occur with a predilection for the side of the body that has the most pronounced bony lesions. The locations of the pigmented spots vary, but the back, buttocks, inner aspects of the thighs, neck and scalp are common sites. In case 4 of our series, a large pigmented spot on the occipital portion of the scalp was the only discolored area of the skin and was associated with alopecia of this same region. Similar localization of pigmentation of the scalp has been observed by others.

OTHER OBSERVATIONS

Laboratory Data—The results of chemical analysis of blood, urine and feces of patients who have Albright's syndrome are usually as follows. Values for serum calcium and serum phosphorus are variable but usually are within the limits of normal. Serum phosphatase is increased, the amount of increase being in general consonant with the degree of activity of the osseous lesions. Studies on calcium balance have varied, in some cases equilibrium has been noted, in some cases a measurable degree of retention and in others a state of so-called negative balance. Excessive excretion of calcium ordinarily is interpreted as

favoring a diagnosis of parathyroid tumor, but in at least 1 case reported in the literature it was associated with polyostotic fibrous dysplasia. Consequently it is doubtful whether the results of calcium studies alone can be the deciding factor in the differential diagnosis of this condition from hyperparathyroidism resulting from hyperplasia or tumor. High values for serum cholesterol occasionally have been reported and have resulted in the mistaken diagnosis of xanthoma of bone. In practically all cases of Albright's syndrome the values for serum cholesterol have been normal. In a few cases of this disease such diversified observations have been reported as decreased dextrose tolerance with or without glycosuria, diminished hepatic function as evidenced by retention of dye, abnormal values for serum protein, elevation of the basal metabolic rate and increased urinary excretion of estrogen. In the majority of cases, however, such evidence has not been obtained, and its seeming importance diminishes when one attempts to apply it generally in the study of Albright's syndrome.

Roentgenologic Characteristics—As a rule, polyostotic fibrous dysplasia has a distinctive roentgenologic appearance, and in most instances the correct roentgenologic diagnosis can be made without difficulty. In most cases several or many bones are affected, but in some cases only one bone or part of a bone is involved. The solitary lesions of bone most frequently cause difficulty in diagnosis. When Albright's syndrome is present, involvement of many bones almost always occurs. Osseous lesions of polyostotic fibrous dysplasia sometimes are limited strictly to one side of the body, but when there is extensive skeletal involvement, the lesions are often bilateral, most of the lesions being on one side. The lower extremities are involved more frequently than the upper extremities. The skull frequently is affected. The lesions are disseminated, and normal bone is present between the regions of abnormal bone. Polyostotic fibrous dysplasia almost always can be distinguished from hyperparathyroidism, because in the latter there is generalized abnormality of bone. The epiphyses are not affected by polyostotic fibrous dysplasia, which is an important consideration in distinguishing this condition from Ollier's disease (dyschondroplasia).

Lesions of polyostotic fibrous dysplasia consist mainly of masses of fibrous tissue which in most instances replace the medullary structures of the involved bone. This leads to thinning of the cortex of the bone from within, and in many cases there is moderate or extreme expansion of the involved bone. These changes result in a distinctive roentgenologic appearance, such as

²³ Albright, F. Personal communication to the authors.

was observed in case 5 (figs 11 and 12). It must be emphasized, however, that at times the lesions of polyostotic fibrous dysplasia may develop subperiosteally, as illustrated by case 4 (fig 9), and thereby cause erosion of the cortex from without. In cases of this type, slight or no expansion of involved bone occurs, and the roentgenologic appearance is considerably different from that of lesions beginning in the medullary portion.

Since in polyostotic fibrous dysplasia the bony structures are replaced by masses of fibrous tissue, the involved portions of bone are abnormally radiolucent. For this reason focal involvement that starts in the medulla and causes expansion of bone may resemble cystic lesions of bone. Localized zones of osteosclerosis frequently are found in association with radiolucent lesions, and in some cases osteosclerosis is most conspicuous.

Bones affected by polyostotic fibrous dysplasia are sometimes abnormally long. When Albright's syndrome is present the growth of bone may be accelerated during childhood, but premature union of the epiphyses may cause an early arrest of growth and resulting dwarfism. When adult life has been reached the lesions of bone no longer progress or progress very slowly.

Pathologic fractures which frequently complicate this condition usually occur through regions of major involvement. Periosteal reaction develops if a pathologic fracture is present, otherwise no periosteal reaction is produced by these lesions. Pathologic fractures often result in shortening and gross deformity of bone. When there is extreme involvement of a bone, multiple fractures may produce a peculiar crumpled appearance. The rapid healing of pathologic fractures indicates that the reparative process proceeds in an orderly fashion.

Lesions of the skull frequently are seen in polyostotic fibrous dysplasia. The changes in the vault, occiput and mandible closely resemble those that occur elsewhere in the skeleton. Frequently expansion of these parts of the skull occurs. Radiolucent zones resembling cysts may be present. Little, if any, osteosclerosis is present in these regions. The lesions affecting the basal portion of the frontal bone and sphenoid, ethmoid and maxillary bones are different from the lesions of fibrous dysplasia as seen elsewhere. In these locations the lesions are almost always osteomatoid in type. The bone is extremely dense and thick. Complete or partial obliteration of the paranasal sinuses frequently is present. Deformity of the orbit with ocular proptosis is not unusual. Obstruction of the nasal passages may

occur. Expansion of the involved bone may result in asymmetry of the skull. Extreme prominence of the forehead, maxilla or mandible is not uncommon.

The osteomatoid thickening of the base of the skull, especially of the wings of the sphenoid bone or of the basal portion of the frontal bone, may simulate the hyperostosis that is associated with meningioma. These lesions of the skull have a superficial resemblance to those seen in Paget's disease, but distinction should not be difficult. The term *leontiasis ossea* is used to designate a type of generalized facial deformity. Almost always, however, this deformity is the result of polyostotic fibrous dysplasia, hence no distinction between the two conditions is necessary.

Pathologic Features—The cortex of the involved bony segments is thinned, and the substantia spongiosa and marrow are filled with fibrous tissue, which may be vascular or avascular. Occasional spicules of degenerating and regenerating bone are found, the latter often being surrounded by normal numbers of osteoblasts. Islands of cartilaginous metaplasia occasionally are observed. Blood pigment sometimes is noted. There is a characteristic paucity of osteoclasts and those present have been described as being abnormal. In other cases, especially around sites of recent fractures, osteoblastic and osteoclastic activity may be pronounced and the picture may simulate that of benign foreign body giant cell tumors of bone. Cysts are not commonly encountered except in regions in which degenerative changes are observed. Foam cells have been described in a few cases, and we have seen them in our own specimens, however, they are usually absent, and differentiation of the condition from xanthoma of bone presents no diagnostic difficulties.

In cases of Albright's syndrome bones that appear normal roentgenographically present a normal appearance on biopsy, but in cases of hyperparathyroidism all sections reveal mild to extreme osteoporosis. Although Jaffe expressed the belief that in cases of Albright's syndrome there is fibrosis of the bone marrow which is not observed in cases of hyperparathyroidism, most investigators are willing to concede that a differential diagnosis cannot be made from biopsy of an isolated fragment of porous bone. Consequently the pathologic interpretation should be considered in conjunction with an evaluation of the clinical history, roentgenographic findings and the results of chemical analysis of the blood.

Pathologic interpretation of the cutaneous lesions has been made possible through biopsy

in a number of cases. The changes have been constant and have paralleled the observations made in 2 of our own cases. The lesion demonstrates an excess of melanin pigment, which sometimes is confined to the basal layer of the epidermis but occasionally extends into the granulosum. There may be a few melanophores in the cutis, but as a rule there are no nests of nevus cells as in the ordinary mole. An associated hypertrophy of the muscular elements comprising the arrectores pilorum recalls the precocious puberty with early appearance of axillary and pubic hair which is observed in some females who have this strange malady.

DIFFERENTIAL DIAGNOSIS

Precocious puberty, which is present in association with a florid or complete form of Albright's syndrome, is a phenomenon that is not associated with parathyroid adenoma. Consequently differential diagnosis should offer few difficulties. Nevertheless in the past the notion that porous bones indicate the presence of hyperparathyroidism has become so fixed that at least 20 patients who had complete or incomplete forms of Albright's syndrome have been submitted to fruitless explorations of the neck in search of a causative tumor. In incomplete forms of the disease, the fact should be borne in mind that hyperparathyroidism is rare in childhood, whereas Albright's syndrome usually dates from an early age. In the former disease patients complain of pain in the bones, profound muscular weakness and digestive disturbances, whereas patients suffering from the latter appear well except for the local disability produced by severe osseous lesions. Generalized pain in the bones is not often encountered. In cases of hyperparathyroidism widespread osteoporosis is present, whereas in Albright's syndrome the osseous lesions are spotty in character and often unilateral in distribution, with roentgenologically normal bone in many regions. Cysts are the exception rather than the rule. Renal lithiasis and fixation of the specific gravity of urine, so commonly found with parathyroid adenomas, are rarely observed with Albright's syndrome.

The high values for serum calcium, low values for serum phosphorus and noticeably negative calcium balance in cases of hyperparathyroidism contrast with the normal values obtained in cases of Albright's syndrome. High values for serum phosphatase may be obtained in both conditions. A pronounced increase in the excretion of calcium as compared with the intake (negative calcium balance) favors a diagnosis of hyperparathyroidism, but one occasionally encounters

a case which proves an exception to this general rule.

The differentiation of Ollier's dyschondroplasia from Albright's syndrome may give rise to some diagnostic difficulties, inasmuch as it too occurs in young persons. The finding of occasional islands of cartilage in the bony lesions of Albright's syndrome heightens this similarity. However, Ollier's disease is a disturbance of chondrification and therefore does not involve bones that are laid down in membrane, such as those of the skull. Moreover, disturbances of the epiphyses are characteristic of Ollier's disease, whereas absence of involvement of epiphyses is a noteworthy feature of Albright's syndrome. Cutaneous pigmentation in both sexes and precocious puberty in females are additional differentiating features of Albright's syndrome.

Osteogenesis imperfecta often presents blue sclera and sometimes certain other hereditary evidences which appear to be of value in differential diagnosis. Blue scleras occasionally have been reported in association with polyostotic fibrous dysplasia.²⁴

Von Recklinghausen's neurofibromatosis, with its characteristic pigmentation of the skin also may be associated with osseous lesions and thus complicate the problem of differential diagnosis. The presence of neurofibromas along the course of cutaneous nerves provides an important clue, and the diagnosis easily can be settled by biopsy. Neurofibromas do not occur in connection with Albright's syndrome.

In locations other than the vertebral bodies, hemangiomas of bone may have certain features in common with polyostotic fibrous dysplasia.²⁵ The value of biopsy in such cases is again obvious. The gross appearance of the two lesions, however, is entirely different.

According to the early literature, xanthomatosis presented problems of differential diagnosis, and several cases of Albright's syndrome have been recorded as typical examples of xanthoma of bone. Involvement of the cranium in cases of Albright's syndrome in young persons may simulate that found in xanthomatosis. Clinical studies on the level of cholesterol and other lipids of the blood may establish the diagnosis in an occasional case. In others biopsy of an osseous lesion will be necessary. Foam cells occasionally are encountered in the bony lesions associated with Albright's syndrome but never

24 Nichols, B. H. *Fragilitas Osseum, Brittle Bones and Blue Sclera, Hereditary Mesenchyme Hypoplasia*, Cleveland Clin Quart 7:58-65 (Jan) 1940.

25 Pierson, J. W., Farber, G., and Howard, J. E. *Multiple Hemangiomas of Bone, Probably Congenital*, J A M A 116:1245-1248 (May 10) 1941.

in the abundance in which they may be present in xanthoma

Biopsy also may be necessary to rule out a diagnosis of metastatic cancer, which was first considered in case 2 of our series. A similar procedure theoretically might be adopted in cases of so-called latent lesions that might be mistaken roentgenologically for certain primary malignant tumors of bone such as multiple myelomas.

Granulosa cell tumor of the ovary produces precocious puberty but usually none of the other features of Albright's syndrome. Adrenal tumors may be recognized by the fact that those producing precocious puberty (cortical) rarely metastasize to bone and those metastasizing to bone (medullary) do not produce precocious puberty.

TREATMENT

In general no specific treatment for Albright's syndrome has been developed. In the cases with extensive osseous involvement the most promising results have followed the use of aluminum acetate as recommended by Helfet. Both clinical and roentgenologic improvement have been noted after the use of this preparation in cases of osteoporosis. Our experience has not been extensive enough to warrant the claim that anything approaching a cure can be obtained by the use of aluminum acetate nor do we know how long the improvement might be sustained.

Treatment with vitamin D and calcium in various forms seems to have produced little or no beneficial effect. Roentgen therapy has been tried from time to time. While in a localized lesion it may produce some sclerosis and fibrosis, its use is contraindicated when the condition is more generalized. In children, extensive irradiation over epiphyses is likely to lead to arrest of epiphyseal growth.

Pathologic fractures should be reduced and splinted in a manner similar to that of any other fracture, and early union usually results. In cases of pathologic fracture in which large cysts occur restoration of the bony substance and healing of the fracture can be hastened by a bone grafting procedure.

In all cases of Albright's syndrome, whether treated by medical or surgical means, we believe that the use of aluminum acetate with at least one pint of milk a day is indicated.

SUMMARY AND CONCLUSIONS

Six new cases of Albright's syndrome were encountered at the Mayo Clinic. These bring the cases reported in the literature to a total of 39. Information concerning these cases and

1 reported by Shallaard has been added to the tabulated review of the literature prepared by Gorham and co-workers in 1942.

The disease occurs more commonly among females than among males and frequently manifests itself early in childhood. Several of our patients were found to have latent lesions in adult life.

In some females who have Albright's syndrome, sexual and somatic development are precocious. In males there may be some evidence of somatic precocity but few sexual changes. In both sexes, but particularly among females, premature arrest of growth may occur. Cutaneous pigmentation accompanies the disease in both males and females.

Extraskkeletal manifestations may occur in the absence of extensive osseous lesions. This observation is contrary to the general impression obtained from the literature. Clinically silent but roentgenologically extensive and active lesions of bone can be present in adults who have Albright's disease. This observation also differs from those recorded in the literature. A tendency in our cases toward unilateral involvement of bones was in harmony with the findings of other investigators. The osseous lesions appeared to be responsible for the major complications of the disease. Symptoms so produced were in general progressive in severity, but remissions and exacerbations, with sometimes long periods of clinical quiescence, were observed.

Pathologically the picture was that of a profound disturbance of metabolism of bone in which decalcification and resorption equaled or exceeded the processes of tissue repair by osteoblasts and fibroblasts. Contrary to previous observations, microscopic examination in our cases occasionally demonstrated brown tumors and cysts. The microscopic resemblance to giant cell tumor in some of our material was also unusual. Accordingly, we agree with those investigators who claim that the diagnosis of Albright's syndrome cannot be made solely on the basis of microscopic studies.

In our series we were unable to see how hepatic disease or thyrotoxicosis played any part in causing this condition. Evidence of a lesion involving the central nervous system was in 1 case equivocal.

Whether chronic hyperphosphatemia existed in these 6 cases is uncertain, but therapy based on this assumption was applied with some success in 1 case. If the results in additional cases are promising, the method should prove of benefit to persons affected with this strange malady.

INFECTIOUS MONONUCLEOSIS

AN ANALYSIS OF THREE HUNDRED CASES WITH THREE CHARACTERIZED
BY RARE HEMATOLOGIC FEATURES

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The variegated clinical manifestations of infectious mononucleosis have been emphasized repeatedly by most writers on the subject in recent years¹. It has also been emphasized that these manifold signs and symptoms often make the diagnosis difficult, because frequently some particular combination of symptoms of the disease will duplicate the important findings of other clinical entities.

We have reviewed a series of 300 cases of infectious mononucleosis observed over the past twenty months at several large air force hospitals, and we also have encountered the same long list of heterogeneous symptoms and signs that have been observed and recorded by other investigators. Moreover, we find that the relative frequency of these manifestations, with but insignificant percentage variations, closely approximates that observed by previous authors. In addition, however, to these manifestations, we have observed in this series 3 cases characterized by a severe anemia with leukopenia and thrombopenia which presented considerable difficulty in diagnosis. Therefore, it was thought worth while to review briefly this rather large series of cases, recording the symptoms and signs, and further to give a more detailed discussion of the 3 cases with the characteristics just referred to.

In this series of 300 cases the complaints of the patients when they were admitted to the hospital were not so variable as the diagnoses made on admission. Tables 1 and 2 illustrate this point.

From the tables it will be noted that the most frequent complaints were sore throat, enlarged lymph nodes, headache and fever. Furthermore,

in only 37 cases in the entire series was the disease correctly diagnosed on the patient's admission to the hospital.

TABLE 1—*Admission Diagnoses*

Diagnosis	Cases
Acute pharyngitis	64
Nasopharyngitis	45
Infectious mononucleosis	37
Acute tonsillitis	36
Atypical pneumonia	19
Acute sinusitis	12
Diagnosis uncertain *	12
Lymphadenitis	10
Bronchitis	10
Malaria	7
Jaundice	6
Cervical myositis	5
Vincent's angina	5
Influenza	4
Epistaxis	4
Gastroenteritis	3
Suspected meningitis	3
Cervical mass	2
Heat exhaustion	2
Reaction to typhoid vaccine	1
Psychoneurosis	1

* These patients were admitted to the hospital for observation.

TABLE 2—*Admission Complaints*

Complaint	Cases
Sore throat	146
Lymphadenopathy	81
Malaise	72
Headache	71
Fever	67
Anorexia	58
Cough	38
Abdominal pain	14
Cutaneous eruption	11
Nausea	9
Vertigo	9
Vomiting	7
Arthralgia	7
Jaundice	6
Epistaxis	6
Myalgia	5

1 Tidy, H. L. Glandular Fever and Infectious Mononucleosis. *Lancet* 2: 180 and 236, 1934. Spark, T. E. H. Infectious Mononucleosis. *Problem in Diagnosis*, M. J. Australia 2: 413, 1942. Werlin, S. J., Dolgopol, V. B., and Stern, M. E. Infectious Mononucleosis, a Diagnostic Problem, *Am J M Sc* 201: 474, 1941.

Many writers have divided infectious mononucleosis into three types, namely, the anginose, the glandular and the febrile. In our series 150 cases were instances of the anginose, 127 of the glandular and 23 of the febrile type.

In all 300 of these cases there was a positive heterophile agglutination in dilutions ranging from 1 to 112 to 1 to more than 10,000

The list of different conditions observed in this series serves to stress the often repeated statement that infectious mononucleosis is a disease of remarkable variability. Table 3 serves to illustrate this point.

The table shows that in 172 cases of this series a generalized adenopathy was observed and in 123 enlarged cervical nodes only were seen. In 67 cases the enlarged nodes were tender. The spleen was palpable in 104 cases and the liver in 47. In 9 cases the patients had generalized petechiae, and in 4 petechiae were found in the oral cavity. In 16 cases

TABLE 3—Positive Signs

Generalized adenopathy	172
Cervical adenopathy only	123
Follicular pharyngitis	112
Palpable spleen	104
Tender adenopathy	67
Palpable liver	47
Tender spleen	39
Gingivitis	37
Membranous pharyngitis	34
Acute tonsillitis	29
Dermatitis	16
Jaundice	11
On admission	6
Petechiae	9
Oral cavity	4
Generalized	9
Nausea	9
Peritonsillar abscess	7
Vomiting	7
Epistaxis	6
Myositis	5
Diarrhea	4
Hemoptysis	3
Abdominal tenderness	3
Mild stupor	3
Stiff neck	2
Delirium	1

dermatitis which was usually either scarlatiniform or macular was noted. In 3 cases the patients had hemoptysis, in 11 they were jaundiced, and in 6 of the latter they were jaundiced on admission. Mild stupor, stiff neck and even delirium were observed in rare instances.

The symptoms and signs seem to fall roughly into four main groups: (1) respiratory, characterized by nasal obstruction, cough, epistaxis, pharyngitis and tonsillitis, (2) gastrointestinal, by nausea, vomiting and abdominal tenderness, (3) hematologic, by hypoplastic and hemolytic anemia as well as thrombopenia and leukopenic neutropenia, and (4) dermatologic, by scarlatiniform or macular rashes as well as pruritus with and without jaundice.

A recent report of a case by Ziegler,² recording the observations at necropsy in a case of

infectious mononucleosis in which rupture of the spleen was the cause of death, sheds considerable light on the pathogenesis of this disease. Moreover, the histologic observations in Ziegler's case may explain the wide variety of signs and symptoms in infectious mononucleosis. Ziegler found focal interstitial infiltrates in the liver and kidneys with proliferation of reticulum cells and necrosis, and it was his opinion that these lesions probably represented "an acute infectious granulomatous process." Furthermore, he observed pulmonary lesions in which there was distention and often obstruction of the alveolar capillaries with mononuclear cells, together with scattered perivascular and interstitial mononuclear infiltrates.

These observations suggest that infectious mononucleosis is an infection which may localize in many tissues and organs.

Since the principal objective of this paper is to discuss the cases with certain rare hematologic features, we will review them briefly. In this entire series of 300 cases there were 6 which were distinguished by moderate to moderately severe anemia. Anemia has always been considered a rare manifestation of infectious mononucleosis and usually has been thought to be due to some complicating factor unrelated to the primary disease. Unfortunately, complete clinical and laboratory studies with thrombocyte counts were carried out in only 3 of the 6 cases in this series.

REPORT OF CASES

CASE 1—A 30 year old white woman entered the hospital because of severe occipital headaches, malaise and loss of appetite.

She was in good health until two weeks prior to her admission, when she noticed that it was becoming difficult to do her daily work. For three days prior to admission she had awakened each morning with a severe occipital headache which grew worse as the day proceeded. A blood count done a week before her admission showed no abnormality.

The past history revealed nothing significant. She had had the usual childhood diseases but no serious illness or operations.

Physical examination showed a well developed woman in no acute distress. There was a fine macular rash on the left side of her face extending from the ear over the left cheek to the side of the mouth, the rash did not fade on pressure. Small discrete nontender cervical lymph nodes were palpable bilaterally. The tip of the spleen was barely palpable.

The blood pressure was 126 systolic and 75 diastolic. The pulse rate was 90, the temperature 100 F and the respiratory rate normal.

Roentgenologic examination revealed that the chest was normal.

2 Ziegler, E. E. Infectious Mononucleosis. Report of a Fatal Case with Autopsy, Arch Path 37:196 (March) 1944.

Examination of the blood showed a red cell count of 3,680,000, a hemoglobin content of 122 Gm and a white cell count of 8,400, of which 75 per cent were lymphocytes, 20 per cent segmented forms, 1 per cent stab forms, 3 per cent monocytes and 1 per cent eosinophils. Reticulocytes numbered 18 per cent, and platelets, 257,600. A heterophile agglutination occurred in a 1 to 792 dilution. Other laboratory results were entirely normal.

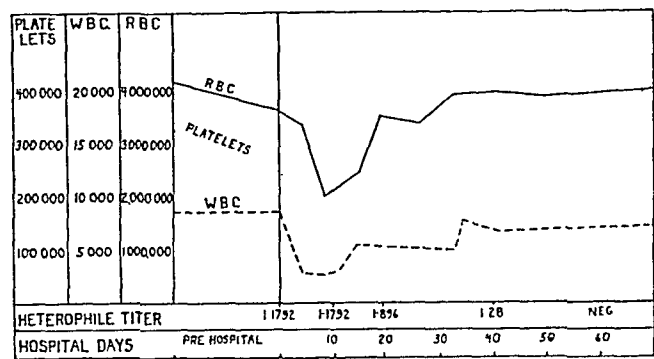


Chart 1—Results of blood counts and heterophile agglutination tests in case 1

The patient was given codeine, 1/2 grain (0.03 Gm), for headache. No other medication was administered.

The clinical course was relatively steady, and the fatigue and malaise grew worse and did not remit until about the eighth day after the patient entered the hospital. From that day on a progressive improvement was noted.

Serial blood counts, platelet and reticulocyte counts and heterophile agglutination tests were done.

The hematologic picture in this case was one of increasing anemia, thrombopenia and leukopenia which gradually returned to normal, the patient being discharged on the nineteenth day in the hospital.

CASE 2—The patient, an active, healthy, 19 year old white youth undergoing training as an aerial navigator, was first seen three days prior to his admission to the hospital, complaining of coryza, sore throat and malaise.

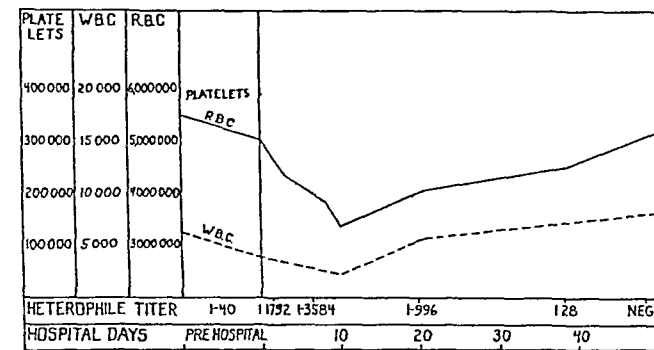


Chart 2—Results of blood counts and heterophile agglutination tests in case 2

At this time physical examination revealed an injected pharynx but otherwise nothing abnormal. A blood count was done, with entirely normal results. On the day of his admission the patient became acutely ill with nausea, vomiting and an extremely sore throat. Examination then revealed generalized small nontender lymph nodes. The spleen and liver were not palpable. A macular rash was noted over the chest and upper part of the abdomen. Hematologic studies at this time

revealed a moderate lymphocytosis, and the heterophile agglutination test elicited a positive reaction in a 1 to 56 dilution.

The patient was put at complete rest in bed and was given a liquid diet. No other therapy was instituted.

On the fourth day after he entered the hospital it was noted that he had a few petechiae over the tibial areas, the trunk and the arms. Repeated counts revealed 250,000 platelets per cubic millimeter and a heterophile agglutination reaction in a 1 to 1,792 dilution. No complaints were noted except malaise, sore throat and a stuffy nose. The spleen was barely palpable at this time.

Daily platelet counts were done, and on his seventh day in the hospital repeated counts revealed a level of 60 to 90,000. The heterophile agglutination occurred in a 1 to 3,984 + dilution. Examination revealed many petechiae over the entire body and a small hemorrhage of the conjunctiva of the left eye and clotted blood in the left nasal cavity.

Symptomatic treatment was continued, and the patient gradually returned to normal, being discharged from the hospital on the twenty-fourth hospital day.

Rechecks revealed a normal hematologic balance and no palpable nodes or spleen.

CASE 3—A 22 year old white naval officer was admitted to the hospital, complaining of severe nausea, shortness of breath and headache. Approximately four

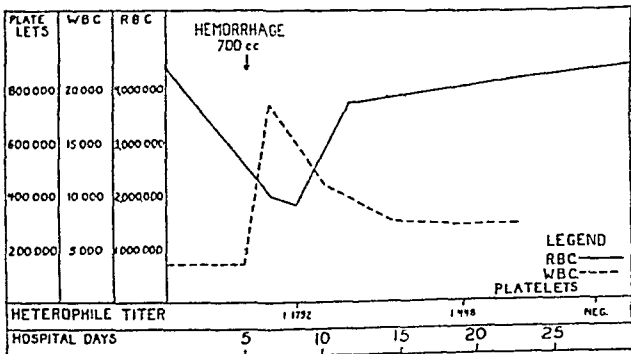


Chart 3—Results of blood counts and heterophile agglutination tests in case 3

hours before his admission he had been overcome by smoke from a smoke generator while he was on maneuvers.

The past history was entirely noncontributory.

Physical examination revealed a well developed white man who was acutely dyspneic. There were two minor abrasions of the scalp over the left parieto-occipital area. The respiratory rate was 32, the chest was symmetric, and expansion was equal. The patient was dyspneic but not cyanotic. The breath sounds were somewhat distant throughout. Occasional subcrepitant rales were heard throughout both pulmonary fields anterior and posterior. The heart sounds were distant, the pulse rate 140.

The patient was given oxygen inhalations and symptomatic treatment consisting of 50 per cent dextrose by vein and theophylline ethylenediamine. On his admission the blood count was normal except for a moderate lymphocytosis, the total white cell count being 4,200.

On his third day in the hospital the patient vomited approximately 700 cc of bright red blood and clots and passed several black stools which contained occult blood. Results of examination were approximately the same as at the time of his admission, except that the spleen and liver were palpable. A blood count at this time showed 2,240,000 erythrocytes, a hemoglobin content of 7.5 Gm,

and a positive heterophile agglutination reaction in a 1 to 1,992 dilution. The patient was given 500 cc of whole blood and 500 cc of plasma. The count steadily declined until the eighth day, when the count revealed 1,900,000 erythrocytes, 100,000 platelets and white blood cells 18,500 with 87 per cent lymphocytes. Heterophile agglutination occurred in a 1 to 1,992 dilution. He was given 1,000 cc of whole blood. The icteric index at this time was 31, the indirect van den Bergh reaction was 3.5.

On the tenth day a generalized macular eruption appeared on the entire abdomen and thorax.

The patient gradually improved, the hematologic picture steadily returned to normal, and the patient was discharged on the fortieth day in the hospital.

The smoke was said to contain no toxic chemical ingredients.

Platelet counts in all 3 cases were made both by the method of Dameshek and by a modified Vilarinho and Pimentel technique.^{2a}

COMMENT

A glance at the charts on these 3 cases shows a rapid and simultaneous drop in red blood cells, white cells and platelets, with a rapidly increasing heterophile agglutination followed by a much more gradual rise in all three of the formed blood elements and a concomitant fall in the heterophile titer.

An interesting feature of these cases is the complete lack of any of the usual clinical manifestations of infectious mononucleosis, and in cases 1 and 2 no toxic factor or other clinical finding was encountered that might account for the rapidly developing anemia, leukopenia and thrombopenia. In case 3 the only possible cause of the illness might have been the inhalation of smoke.

These 3 cases may serve to emphasize the fact that a differential diagnosis between leukemia and infectious mononucleosis cannot be made on the absence of anemia plus the presence of immature lymphocytes alone. Furthermore, the diagnosis cannot depend on the additional presence of a positive heterophile antibody agglutination, since Kent³ has reported a case of rapidly fatal monocytic leukemia in which a high and rapidly increasing heterophile agglutination titer was present. One of us (F C H) had the opportunity to study this case, and it was a classic example of leukemia with widespread heteroplastic infiltrates. Even though a positive heterophile agglutination reaction is rare except in patients with infectious mononucleosis and in patients recently treated with horse serum, it

does sometimes appear in those with leukemia. Hence, the presence of abnormal though chiefly mature lymphocytes in association with a positive reaction to a Paul-Bunnell test does not, as many laboratory technicians think, clinch the diagnosis of infectious mononucleosis. Therefore, the necessity exists for careful and painstaking morphologic studies of the blood in certain bizarre cases of infectious mononucleosis.

We can only hypothesize as to the cause of this apparently rare triad of complications of infectious mononucleosis which we have just presented. It is our belief that any of these complications may occur singly. Certainly leukopenia is not at all rare. We were able to find, however, records of but few cases of proved thrombopenic purpura from infectious mononucleosis in the literature.⁴ A study of Magner's case shows that no platelet counts were made and a paucity of platelets on the stained film was the only evidence of thrombopenia submitted. Anemia as a complication of infectious mononucleosis, though rarely recorded, is occasionally observed, and it is quite possible that thrombopenia might be found more frequently if in all cases in which petechiae are encountered platelet counts are performed.

The anemia has been ascribed to a hemolytic process,⁵ and it has been more or less dogmatically stated that "anemia does not occur in uncomplicated cases" of infectious mononucleosis.⁶ It is our belief that the anemia may also result from an infiltration of the bone marrow, with a resultant depression of all the formed blood elements. Freeman,⁷ studying surgical biopsy specimens of the bone marrow in infectious mononucleosis, has apparently demonstrated such an infiltration. Moreover, it does not seem unreasonable to assume such an infiltration in view of the observations by Ziegler, in whose case visceral infiltrative lesions were encountered. Furthermore, Kilham and Steigman⁸ found infiltrates similar to those of Ziegler in biopsy specimens of the liver. If such an infiltration should be the cause of the anemia, leuko-

4 Magner, W., and Brooks, E. F. Infectious Mononucleosis with Acute Thrombopenic Purpura, *Canad. M. A. J.* **47**: 35, 1942. Loyd, P. C. Acute Thrombopenic purpura in Infectious Mononucleosis, *Am. J. M. Sc.* **207**: 620, 1944.

5 Moore, C. Personal communication to one of us (J. T. R.).

6 Wintrobe, M. M. *Clinical Hematology*, Philadelphia, Lea & Febiger, 1942, p. 746.

7 Freeman, W. Bone Marrow Studies in Glandular Fever, *Am. J. Clin. Path.* **6**: 185, 1936.

8 Kilham, L., and Steigman, A. J. Infectious Mononucleosis, *Lancet* **2**: 452, 1942.

2a Copley, A. L., and Robb, T. P. Studies on Platelets. I. Method of Vilarinho and Pimentel and a New Direct Method of Counting Blood Platelets, *Am. J. Clin. Path.* **12**: 362, 1942.

3 Kent, C. F. "False" Positive Paul Bunnell (Heterophile) Reaction? *Am. J. Clin. Path.* **10**: 576, 1940.

penia and thrombopenia in these cases that we have recorded, the lesion in the bone marrow is probably more in the nature of a focal infectious granulomatous process than a simple heteroplastic infiltration. At least this is our belief.

CONCLUSIONS

Three hundred cases of infectious mononucleosis were observed, and the usual long and varied list of clinical findings were encountered. Only cases showing a positive heterophile agglutination reaction were included in this series.

In 6 cases the patients had anemia, and in 3 of this group there were leukopenia and

thrombopenia which came on rapidly. In none of these 3 cases were any of the usual clinical manifestations of infectious mononucleosis present, with the exception of mild adenopathy.

It is hypothesized that this triad of hematologic findings may have been due to depression of the activity of the bone marrow resulting from an infectious granulomatous process involving the marrow. It is further hypothesized that such a pathologic process may also be the underlying cause for the disturbances of the central nervous system and for the pulmonary, gastrointestinal and hepatic manifestations which are sometimes seen in infectious mononucleosis.

AZOTEMIA ASSOCIATED WITH GASTROINTESTINAL HEMORRHAGE

AN EXPERIMENTAL ETIOLOGIC STUDY

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Many workers¹ have confirmed the original observations of Sanguinetti² that an elevation of the nitrogen content of the blood may be associated with gastroenteric bleeding. Opinions concerning the pathogenesis of this condition are not in agreement. Sanguinetti² attributed the azotemia to absorption of protein from the intestine,

From the Departments of Medicine and Pharmacology, The University of Texas School of Medicine

Hoffman-LaRoche, Inc, supplied the heparin used in these studies

1 (a) Christiansen, T. Uraemia as Cause of Death in Massive Hemorrhage from Peptic Ulcer, *Acta med Scandinav* **85** 333-345, 1935. (b) Meyler, L. Post-haemorrhagic Uraemia, *ibid* **87** 313-325, 1935. (c) Alsted, G. Further Studies on Azotemia Following Hemorrhage in the Digestive Tract, *Am J M Sc* **192** 199-208, 1936. (d) Meyler, L. Uraemia Due to Dehydration, *Acta med Scandinav* **90** 475-488, 1936. (e) Sucic, D. Akute Azotämie bei grossen gastrointestinalen Blutungen, *Klin Wchnschr* **14** 1316-1318, 1935. (f) Schiff, L, and Stevens, R J. Elevation of Urea Nitrogen Content of the Blood Following Hematemesis or Melena, *Arch Int Med* **64** 1239-1251 (Dec) 1939. (g) Stevens, R J, Schiff, L, Lublin, A, and Garber, E S. Renal Function and the Azotemia Following Hematemesis, *J Clin Investigation* **19** 233-237, 1940. (h) Schiff, L, Stevens, R J, Goodman, S, Garber, E, and Lublin, A. Observations on the Oral Administration of Citrated Blood in Man. I The Effects on the Blood Urea Nitrogen, *Am J Digest Dis* **6** 597-602, 1939. (i) Kaump, D H, and Parsons, J C. Extrarenal Azotemia on Gastro-Intestinal Hemorrhage. I General and Clinical Consideration, *ibid* **7** 189-190, 1940. (j) II Experimental Observations, *ibid* **7** 191-194, 1940. (k) Chunn, C F, and Harkins, H N. Experimental Studies on Alimentary Azotemia. I Role of Blood Absorption from Gastro-Intestinal Tract, *Surgery* **9** 695-705, 1941. (l) Alimentary Azotemia Due to Whole Blood Absorption from the Gastro-Intestinal Tract, *Proc Soc Exper Biol & Med* **45** 569-571, 1940. (m) Chunn, C F, Harkins, H N, and Boals, R T. Experimental Studies on Alimentary Azotemia. III Site of Blood Absorption, *Surgery* **11** 56-62, 1942. (n) Yuile, C L, and Hawkins, W B. Azotemia Due to Ingestion of Blood Proteins. Blood Urea Increase Related to Ingestion of Whole Blood, Red Cells, Plasma and Other Proteins, *Am J M Sc* **201** 162-167, 1941. (o) Johnson, J B. The Pathogenesis of Azotemia in Hemorrhage from the Upper Gastro-Intestinal Tract, *J Clin Investigation* **20** 161-168, 1941. (p) Crohn, B B, and Lerner, H H. Gross Hemorrhage as a Complication of Peptic Ulcer, *Am J Digest Dis* **6** 15-22, 1939. (q) Wood, L J. Treatment of Hemorrhage, *Brit M J* **2** 115-

augmentation of general metabolism and chloropenia. Alsted^{1c} studied the condition in patients and suggested blood pressure effects and intestinal absorption as possible causes. Bookless^{1s} expressed the belief that the elevated blood urea levels were mainly due to rapid breakdown of tissue protein. Black^{1r} suggested and Johnson^{1o} stated that azotemia does not occur in patients in the absence of reduction in renal function. The former believed the evidence inadequate to establish renal impairment as the causal mechanism. Stevens, Schiff, Lublin and Garber^{1s} reported that elevation of blood urea associated with gastrointestinal bleeding was not due to impairment of renal function in the absence of shock. Christiansen^{1a} attributed the azotemia to an intoxication from blood stagnating in the intestinal canal. Harkins and co-workers^{1i, m} studied the problem by giving beef blood to dogs. They proposed a new term, "alimentary azotemia," and concluded that azotemia is due to absorption of digested blood and that starvation, dehydration, bleeding, hypochloremia and shock did not play a major part in its production. Yuile and Hawkins¹ⁿ presented conclusions in essential agreement with those of Harkins. They emphasized the role of absorption of digested blood as the cause and stressed that comparable amounts of protein in the form of red blood cells, plasma, casein or lean meat cause similar increases.

At least two writers, Bookless^{1s} and Alsted,^{1c} have expressed the belief that the patients with the most pronounced azotemia are clinically uremic. Values of 190 and 216 mg per hundred cubic centimeters of urea were obtained for 2

121, 1936. (r) Black, D A K. Urea Clearance in Hematemesis, *Lancet* **1** 323-325, 1939. (s) Bookless, A S. Uremia After Hemorrhage, *Guy's Hosp Rep* **88** 22-33, 1938. (t) Glass, J. Untersuchungen über die experimentelle Chlorverarmung, ihre Folgen und die Ursache des Dechlorurationsstodes (Zugleich ein Beitrag zur Frage der Dechlorurationsurämie und der erweissenschützenden Wirkung des Kochsalzes), *Ztschr f d ges exper Med* **82** 776-805, 1932.

2 Sanguinetti, L V. Azoemias en el curso de las hemorragias retenidas a nivel del tubo digestivo (estudio clínico y experimental), *Arch argent de enferm d ap digest y de la nutrición* **9** 264-287, 1934.

patients While this viewpoint may be criticized on the basis that most modern opinions of the pathogenesis of uremia discredit any likelihood that retention of urea is responsible for the azotemia, the beliefs have been expressed and need answering at least to the extent of indicating whether treatment is needed for the elevated nitrogen level, and if so, what treatment It is obvious that an understanding of the mechanism of the condition under discussion must be the basis for intelligent therapy

Because of the disagreements referred to and the implications regarding therapy, this problem has been investigated again

PLAN OF STUDY

All studies were made on dogs, 66 animals in all being employed The study was made on experimental animals because we believe that it would be difficult, if not impossible, to evaluate the relative part played by several factors all of which might be present simultaneously in a given patient Accordingly, we considered the various possibilities which might cause azotemia in a clinical case of bleeding from the upper part of the gastrointestinal tract We have therefore experimentally evaluated each possibility separately and several combinations of possible causes The causes considered and studied were (1) absorption of digested protein from the intestine, (2) effects of low blood pressure alone, (3) combinations of the preceding causes, (4) anemia, (5) dehydration as a result of deprivation of water and (6) renal damage due to absorption of some breakdown product of the blood in the intestine

The dogs were fed well on Purina Dog Chow ^{2a} for several days and were then deprived of food for twelve to fifteen hours prior to the beginning of the observations The experiments were controlled by estimating the values for blood urea nitrogen on 4 fasting dogs over twenty-eight hours and by giving 3 dogs respectively 14, 20 and 284 Gm of homologous blood per kilogram of body weight by stomach tube and by giving 1 dog 13 Gm of meat per kilogram The blood urea nitrogen values were followed at various intervals up to twenty-two hours after the feeding, when they had returned to normal The effect of blood in the gastrointestinal tract was studied by withdrawing blood rapidly from the external jugular vein, citrating it with

2a Following is the formula for Purina Dog Chow Checkers used in this experimental work

	Per Cent
Protein	22.50
Fat	5.50
Fiber	3.75
Ash	7.00
Carbohydrates (nitrogen free extract)	50.25
Moisture	11.00
Calcium	1.75
Phosphorus	1.00
Magnesium	0.11
Potassium	0.70
Soluble chlorides (as NaCl)	1.25
	Parts/Million
Iron	180.00
Copper	8.00
Cobalt	0.10
Manganese	75.00
Carotene	1.70

2.5 cc of 10 per cent sodium citrate per hundred cubic centimeters of blood of one dog and giving it by stomach tube to another dog When the combined effects of low blood pressure and absorption of digested protein were studied, blood was withdrawn from the jugular vein, citrated and given to the same dog by stomach tube A uniform dose of 30 cc of blood per kilogram was used in all experiments in which blood was fed It is realized that this represents a large hemorrhage The amount was deliberately made large with the belief that if results were not obtained with such amounts they would not be obtained with smaller amounts and with the knowledge that dogs withstand loss of large amounts of blood relatively safely Lowered blood pressures were produced by puncture of the external jugular vein The blood pressure was lowered to various levels, usually to 80 mm of mercury or below Thirty per cent of the calculated blood volume was removed initially One to three additional bleedings were required to lower the blood pressure sufficiently in some animals The blood volume was estimated as 8 per cent of the body weight Blood pressures were determined by direct puncture of a femoral artery according to our modification of the method of Dameshek and Loman ³ The effects of anemia were studied by following the blood urea nitrogen level in dogs made acutely anemic by bleeding and by giving blood from other dogs (30 cc per kilogram) to dogs made severely anemic by previous bleeding The effects of dehydration were noted by withholding water from twelve to twenty-four hours, during which time blood had been fed, the blood pressure lowered or these two procedures combined, and comparing the results obtained after the same procedures and after water had been given by stomach tube Strangely, many of the dogs did not appear thirsty even after extreme hemorrhage—contrary to clinical experience with bleeding patients The possible factor of the absorption from the intestine of a substance toxic to the kidney was studied by determining urea clearance before and during a period of digestion of blood This was done during periods of normal and of low blood pressure Urea clearance was also studied on some dogs with blood pressures lowered by bleeding Studies of urea clearance were done by the method and standards of Summerville, Hanzal and Goldblatt ⁴ and determinations of urea were made by standard urease methods ⁵

Hematocrit studies and determinations of the specific gravity of both heparinized whole blood and heparinized plasma were performed routinely on all dogs to be sure our results were not complicated or confused by fluid shifts The specific gravity of whole blood and of plasma was studied by the "falling drop" method of Barbour and Hamilton ⁶

3 Dameshek, W, and Loman, J Direct Intra-Arterial Blood-Pressure Readings in Man, *Am J Physiol* **101** 140-148, 1932

4 Summerville, W W, Hanzal, R F, and Goldblatt, H Urea Clearance in Normal Dogs, *Am J Physiol* **102** 1-8, 1932

5 Van Slyke, D D, and Cullen, G E, in Peters, J P, and Van Slyke, D D Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932

6 Barbour, H G, and Hamilton, W F The Falling Drop Method for Determining Specific Gravity, *J Biol Chem* **69** 625-640, 1926

RESULTS

I Control studies

Four fasting dogs were studied over a period of twenty-four to thirty hours to determine the effect on blood urea levels. The results are recorded in table 1. These results show some indi-

TABLE 1—Control Blood Urea Nitrogen Values

Dog No	Weight, Kg	Hemato crit, %	Blood Urea Nitrogen, Mg /100 Cc				
			Initially	After 4 Hr	After 21 Hr	After 26 Hr	After 28 Hr
9	12.0	41	16.1	23.8	22.0	24.5	23.4
10	10.0	40	12.6	18.2	16.8	16.5	14.0
11	12.6	44	15.4	17.5	13.3	16.1	18.8
12	13.4	44	16.1	14.7	14.7	13.6	13.3

vidual variations but in general show uniformity throughout the period of observation. They may be criticized on the ground that sampling was perhaps at too infrequent intervals.

In these experiments the animals were given 30 cc of blood per kilogram in two equally divided doses, the second dose given two and one-half to three hours after the first. Care was observed to obtain dogs that were not unusually anemic and estimations of hematocrit values and specific gravity of whole blood and of plasma were made.

From these data it can be seen that the urea nitrogen level of the blood invariably rises after the giving of blood by stomach tube. The elevation is apparent within an hour after the blood has been given, the level is well elevated within two to three hours, has reached a peak in about six hours and has returned to within approximately normal range within twelve hours.

While the time relationships of the blood urea nitrogen elevation are uniform, the extent of the elevation is decidedly lacking in uniformity.

TABLE 2—Effect of Variable Amounts of Blood and Meat on Blood Urea Nitrogen Levels

Dog No	Weight, Kg	Blood per Kg, Cc	Meat per Kg, Gm	Blood Urea Nitrogen Mg per 100 Cc								
				Fasting	After Giving of Blood or Meat *							
					(0 30)	(1 35)	(3 0)	(4 38)	(10 50)	(18 0)	(22 25)	(26 45)
2	17.2	14.0		9.5	10.3	13.7	18.9	23.8	14.7	10.9	10.9	8.1
4	9.5	23.4		12.6	(0 40)	(2 15)	(4 20)	(6 20)	(8 12)	(11 57)	(21 55)	
					14.7	27.2	35.7	39.3	30.8	21.3	14.9	
5	12.5	20.0		12.7	(1 17)	(2 55)	(4 30)	(6 20)	(8 55)	(13 10)	(22 25)	
					15.1	28.7	37.0	33.5	23.11	19.6	12.0	
2	17.0		13	13.9	(0 45)	(2 20)	(4 14)	(6 18)	(8 11)	(11 55)	(21 55)	
					11.6	14.0	15.4	16.4	14.4	12.3	12.0	

* The figures in parentheses indicate the time (hours minutes) after blood or meat was given.

Control experiments were also done to show the relation of the effects of various amounts of blood and the similar effects obtained by feeding meat. Table 2 contains the data obtained. These data show that the rise begins within thirty minutes after the blood is given, reaches its peak from four and one-half to six hours after ingestion of blood and returns to within normal range in approximately twelve hours, although approximately eighteen hours is required for its return to fasting levels.

Table 2 also shows that the elevation of blood urea nitrogen following ingestion of meat is of the same character as that obtained from ingestion of blood. The rise following ingestion of meat, lesser by comparison, is due to the fact that 13 Gm of meat per kilogram contains considerably less protein than 14 cc of blood per kilogram.

II Effect of feeding blood on the blood urea nitrogen level

Table 3 contains the data obtained from a study of 6 dogs fed blood and not allowed water for the first twenty-four hours of the experiment.

despite the fact that a uniform dose of blood was given to all dogs. This dose was large, 30 cc of blood per kilogram. But in spite of this the elevation of blood urea nitrogen is not always great (dogs 60 and 62).

The results of hematocrit studies and determinations of specific gravity on blood and plasma indicate that the increase in the blood urea values are probably not due to fluid shifts such as might concentrate the blood components. These values show the reverse, if anything. In all 6 dogs of this group there was a consistent fall in the hematocrit values and specific gravity of whole blood and plasma. The significance of this apparent dilution of the blood is difficult to understand in view of the restriction of water during the first twenty-four hours. Conceivably it could be due to absorption of the water in the blood itself and the water resulting from the metabolism of the digested protein. The decrease in the specific gravity of the plasma may also be contributed to by the fact that blood plasma proteins are being consumed for metabolic needs.

TABLE 3—Effects of Ingested Blood on Urea Nitrogen Levels

No Water for First Twenty Four Hours

	Interval After First Bleeding		Blood Fed, Cc *	Blood Urea Nitrogen, Mg /100 Cc	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm Hg	Urea Clearance, Cc /Min
	Hr	Min				Blood	Plasma		
Dog 17 Weight, 13 Kg	Control		195	8.7	32.4	1.0470	1.0223		
	3	28	195	18.9	35.2	1.0490	Lost		
	6	28		23.5	34.7	1.0473	1.0232		
	9	7		21.2	32.2	1.0466	1.0227		
	12			15.5	30.5	1.0442	1.0227		
	19	47		12.9	34.9	1.0481	1.0220		
	24	10		11.5	30.0	1.0458	1.0227		
	28	22		12.5	31.0	1.0452	1.0231		
	35	45		10.5	31.7	1.0464	1.0228		
	45	85		9.8	32.2	1.0459	1.0231		
Dog 18 Weight, 15 Kg	Control		210	11.8	35.2	1.0539	1.0279		
	3	17	207	23.8	34.8	1.0535	1.0284		
	6	17		32.2	30.7	1.0503	1.0281		
	8	57		26.0	33.2	1.0573	1.0276		
	11	48		19.7	29.7	1.0495	1.0276		
	19	39		14.4	32.5	1.0508	1.0276		
	23	59		14.0	29.9	1.0495	1.0268		
	28	13		12.6	32.7	1.0514	1.0273		
	35	37		14.0	32.7	1.0517	1.0271		
	45	49		12.6	33.5	1.0515	1.0272		
Dog 22 Weight, 11.4 Kg	Control		171	13.3	50.0	1.0612	1.0254		
	2	3	171	35.7	49.8	1.0612	1.0262		
	4	22		41.5	47.2	1.0592	1.0262		
	7			50.0	43.4	1.0564	1.0253		
	9	49		40.0	47.0	1.0572	1.0256		
	12	44		26.6	44.5	1.0574	1.0250		
	23	58		19.0	44.8	1.0578	1.0252		
	30	54		12.6	44.4	1.0548	1.0235		
	36	46		11.9	38.0	1.0506	1.0226		
	47	18		13.3	45.0	1.0554	1.0237		
Dog 58 Weight, 7.7 Kg	Control		116	13.3	46.4	1.0553	1.0233	124	36.8
	2		116	17.3	38.9	1.0505	1.0225	132	
	4	27		23.1	39.0	1.0507	1.0226		
	5	19		22.8	43.8	1.0536	1.0229		
	6	23		20.7	39.0	1.0500	1.0223		
	7	22		15.4	38.0	1.0497	1.0227		36.1
	9	42		10.5	37.0	1.0491	1.0226		
	12	49		6.9	39.3	1.0511	1.0220	126	
	22	31		6.7	43.0	1.0538	1.0233		
	28	50		7.7	34.0	1.0466	1.0219		
	47	1		7.5	41.0	1.0577	1.0231	116	
	48			6.7	39.0	1.0500	1.0226		42.8
	49	4		5.9	39.5	1.0509	1.0224		
Dog 60 Weight, 7.9 Kg	Control		119	9.5	34.0	1.0478	1.0229	104	75.8
	1	51	119	8.5	32.8	1.0473	1.0225		
	4	1		15.2	34.5	1.0475	1.0234		
	4	55		11.6	33.5	1.0477	1.0228		
	5	55		12.8	31.0	1.0442	1.0216		
	7	3		11.9	30.0	1.0436	1.0213		49.7
	9	22		3.5	29.3	1.0432	1.0212		
	11	53		2.1	28.0	1.0431	1.0211	106	
	22	16		2.1	32.0	1.0441	1.0209	107	
	26	14		3.2	29.8	1.0432	1.0200	103	
	27	18		2.8	28.4	1.0426	1.0196		84.2
	28	24		2.9	27.8	1.0427	1.0196		
Dog 62 Weight, 4.6 Kg	Control		69	5.7	33.9	1.0559	1.0236		67.2
		55		8.4	31.2	1.0479	1.0231	129	
	2	12	69	12.2	32.5	1.0479	1.0227	130	
	4	37		11.8	31.2	1.0427	1.0221		
	5	15		12.7	28.5	1.0389	1.0216	134	
	6	14		11.0	29.4	1.0434	1.0217		
	7	11		10.1	28.0	1.0422	1.0215		
	8	48		8.3	28.0	1.0424	1.0217		51.7
	12	17		5.6	28.0	1.0428	1.0213	138	
	22	44		3.8	26.0	1.0420	1.0220	124	
	27	25		5.6	28.0	1.0430	1.0220	132	
	28	22		6.8	27.7	1.0428	1.0215		
	29	31		5.9	27.2	1.0426	1.0216		48.8
	48	45		6.3	26.3	1.0422	1.0218	119	
	49	45		6.0	25.2	1.0416	1.0218		

* Total dose of blood (30 cc per kilogram of body weight) fed by stomach tube in two doses of 15 cc per kilogram

TABLE 4—*Effects of Lowered Blood Pressure by Bleeding on Blood Urea Nitrogen Levels*
No Water Given During First Twelve to Twenty Four Hours

	Interval After First Bleeding		Bled, Cc	Blood Urea Nitrogen, Mg /100 Cc	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm Hg	Urea Clearance, Cc /Min
	Hr	Min				Blood	Plasma		
Dog 15 Weight, 9.8 Kg	Control		215	12.6	48.3	1.0609	1.0292	120	
	2	35	105	16.1	45.5	1.0571	1.0284	110	
	4	36	85	18.3	45.0	1.0546	1.0273	100	
	8			25.6	43.0	1.0526	1.0271	60	
	10	50	(52%)*	31.0	41.3	1.0523	1.0272	60	
	13	42		33.0	40.0	1.0516	1.0274	70	
	22	4		26.8	32.7	1.0455	1.0263	92	
	25	58		24.0	31.0	1.0472	1.0256	102	
	30	40		19.6	28.7	1.0449	1.0256		
	37	30		14.3	21.9	1.0443	1.0251		
	47	50		11.2	25.5	1.0438	1.0259	102	
Dog 16 Weight, 13.9 Kg	Control		285	1.0	42.0	1.0556	1.0254	140	
	2	19	150	13.3	31.8	1.0450	1.0226	126	
	4	16	140	16.1	25.2	1.0391	1.0220	110	
	7	30	90	15.4	33.1	1.0445	1.0232	100	
	10	15	65	16.1	30.3	1.0432	1.0229	106	
	13	15		16.1	29.7	1.0425	1.0223	86	
	21	13	(65.5%)*	16.8	24.2	1.0384	1.0233	90	
	25	27		13.0	25.2	1.0426	1.0239	120	
	29	49		13.9	22.3	1.0390	1.0236		
	37			11.2	25.8	1.0422	1.0241		
	47	14		9.1	26.0	1.0428	1.0249	120	
Dog 19 Weight, 14 Kg	Control		255	13.3	50.1	1.0614	1.0239	160	
	2	3	200	14.0	45.5	1.0568	1.0227	152	
	4	13	100	15.4	39.3	1.0504	1.0212	120	
	6	48	100	15.8	36.8	1.0490	1.0209	110	
	9	38	95	17.8	35.6	1.0484	1.0212	92	
	13	45		20.0	36.4	1.0489	1.0213	73	
	23	59	(65%)*	15.8	29.5	1.0450	1.0216	97	
	31			14.0	26.2	1.0401	1.0206		
	36	47		14.7	22.0	1.0381	1.0204	90	
	47	15		8.8	19.8	1.0372	1.0212	96	
Dog 21 Weight, 12.3 Kg	Control		260	12.6	44.0	1.0582	1.0266	160	
	2	1	195	15.1	40.2	1.0535	1.0248	160	
	3	58	200	17.5	37.1	1.0507	1.0242	130	
	6	35	90	21.0	37.0	1.0507	1.0244	96	
	9	14		23.8	33.0	1.0484	1.0241	76	
	13	17	(76%)*	38.5	32.5	1.0488	1.0246	72	
	23	33		38.5	27.7	1.0458	1.0250	110	
	30	28		25.8	24.0	1.0405	1.0229		
	36	21		19.6	25.0	1.0406	1.0243	105	
	46	58		6.4	19.3	1.0385	1.0229	146	
Dog 53 Weight, 9.7 Kg	Control		225	14.6	53.0	1.0628	1.0268	166	57.9
		56	160	13.7	52.8	1.0612	1.0252	148	
	2	20		16.8	49.5	1.0565	1.0240	67	
	3	26	70	19.8	47.5	1.0558	1.0242	78	
	4	56		21.0	44.0	1.0541	1.0240	50	
	7	10	(58.6%)*	27.8	40.0	1.0550	1.0240	50	
	8	42		28.9	42.5	1.0545	1.0245		
	9	53		33.1	42.0	1.0538	1.0242	51	0
	12	26		38.4	38.0	1.0502	1.0230	53	
	22	20		37.1	32.1	1.0481	1.0239	80	
	27	35		28.0	30.0	1.0459	1.0237	92	
	28	43		34.0	28.0	1.0436	1.0225	92	25.8
	35	13		26.8	25.0	1.0424	1.0231	94	
	46	42		17.5	23.0	1.0421	1.0238	108	
	47	47		17.5	21.3	1.0408	1.0231		25.1
Dog 55 Weight, 11 Kg	Control		245	5.6	44.4	1.0567	1.0261	146	57.3
	1	2	190	7.7	37.0	1.0505	1.0238	118	
	2	3	45	13.3	34.7	1.0470	1.0228	67	
	3	34		17.5	34.0	1.0470	1.0233	62	
	5	40	50	21.2	33.5	1.0472	1.0235	72	
	7	22		18.2	30.0	1.0450	1.0231	56	
	9	2	(60%)*	28.0	30.0	1.0441	1.0233	53	
	10			27.3	28.2	1.0434	1.0230	57	0
	12	46		26.3	27.0	1.0427	1.0233	64	
	23	23		24.2	23.2	1.0389	1.0234	95	
	28	56		12.6	19.9	1.0381	1.0237	95	
	30	1		7.6	20.2	1.0369	1.0235		24.5
	52	9		7.0	18.8	1.0372	1.0244	112	
	53	9		4.2	18.5	1.0372	1.0244		29.7
Dog 57 Weight, 9 Kg	Control		216	10.5	37.2	1.0488	1.0227	121	41.1
		56	100	11.5	30.0	1.0425	1.0204	108	
	2	4	40	10.8	27.7	1.0399	1.0199	67	
	3	42	50	13.7	26.0	1.0384	1.0199	70	
	5	22		20.9	23.0	1.0351	1.0194	62	
	7	24	30	20.4	21.5	1.0336	1.0189	66	
	8	49		19.1	19.5	1.0319	1.0186	58	2.3
	9	49	(60.5%)*	19.9	18.2	1.0313	1.0186	61	
	12	58		26.1	15.8	1.0308	1.0186	60	
	22	50		30.9	13.9	1.0296	1.0195	61	
	27	50		19.8	13.0	1.0292	1.0198	64	
	28	53		20.8	13.0	1.0287	1.0197		16.1
	46	52		10.1	12.0	1.0286	1.0206	96	
	47	58		9.2	11.5	1.0287	1.0206		
	49	5		9.6	11.4	1.0287	1.0206		27.4

* Total per cent of calculated blood volume removed

TABLE 5—*Effects of a Combination of Feeding Blood and Low Blood Pressure (Produced by Bleeding) on Blood Urea Nitrogen Levels*

	Interval After First Bleeding		Bled, Cc	Fed Blood, Cc	Blood Urea Nitrogen, Mg /100 Cc	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm Hg	Urea Clearance, Cc /Min
	Hr	Min					Blood	Plasma		
Dog 27 Weight, 8.4 Kg	Control		225	126	17.4	46.3	1.0577	1.0260	140	
	1	57	150	126	23.8	37.0	1.0492	1.0224	128	
	4	5	100		31.5	28.3	1.0418	1.0203	117	
	6	30			35.7	25.4	1.0397	1.0204	65	
	9	30	45		34.3	25.4	1.0394	1.0218	80	
	13	41			34.3	22.8	1.0375	1.0210	72	
	23	33			27.3	19.9	1.0356	1.0216	92	
	31	10			19.7	16.0	Clot	1.0216	101	
	37	13			17.0	16.0	1.0331	1.0219	114	
	47	35			13.4	15.5	1.0321	1.0226	104	
Dog 28 Weight, 11.5 Kg	Control		225	170	11.9	47.1	1.0582	1.0261	137	
	2		150	173	12.6	40.0	1.0526	1.0241	132	
	3	50	125		11.2	36.4	1.0484	1.0226	107	
	6	4	120		12.6	31.8	1.0451	1.0216	96	
	9	20	60		15.4	28.8	1.0422	1.0216	78	
Animal found dead next morning										
Dog 29 Weight, 9.8 Kg	Control		230	147	27.3	34.0	1.0476	1.0243	130	
	2	5	150	147	27.3	27.0	1.0407	1.0221	114	
	4	25	100		30.8	22.5	1.0367	1.0207	85	
	6	41	60		30.9	23.4	1.0363	1.0213	80	
	9	45	60		37.2	21.5	1.0338	1.0215	80	
	13	9			55.0	17.0	1.0311	1.0209	45	
Dog died during night										
Dog 30 Weight, 9.5 Kg	Control		225	143	14.0	32.9	1.0490	1.0248	140	
	2	10	150	143	22.4	30.0	1.0450	1.0225	98	
	4	25	100		28.8	22.6	1.0285	1.0212	86	
	6	45	55		41.0	22.2	1.0275	1.0215	70	
	9	45	50		48.0	22.3	1.0379	1.0220	75	
	12	35			52.0	20.0	1.0355	1.0220	65	
	22	40			44.0	17.5	1.0351	1.0224	72	
	29	40			29.0	15.3	1.0330	1.0223	80	
	36	25			14.0	14.8	1.0316	1.0220	90	
	47	45			9.0	13.8	1.0316	1.0224	88	
	54	35			9.3	13.0	1.0309	1.0224	92	
Dog 31 Weight, 9.5 Kg	Control		254	171	13.4	51.2	1.0610	1.0266	152	
	1	50	125	131	24.6	32.4	1.0468	1.0218	112	
	4	3	70		50.0	32.7	1.0450	1.0207	96	
	5	58	50		69.0	28.7	1.0406	1.0201	90	
	9	10	40		50.0	25.3	1.0394	1.0206	76	
	12	52	30		73.5	23.2	1.0384	1.0209	76	
	22	5			36.3	22.5	1.0376	1.0225	80	
	29	46			20.2	20.5	1.0359	1.0229	100	
	36	8			13.4	17.9	1.0338	1.0222	92	
	46	40			11.9	21.0	1.0368	1.0240	96	
Dog 32 Weight, 7.8 Kg	Control		220	117	8.7	34.7	1.0498	1.0265	120	
	1	45	100	127	15.0	28.2	1.0433	1.0233	100	
	3	48	55		24.6	26.7	1.0413	1.0221	85	
	5	40			36.5	23.6	1.0386	1.0223	70	
	8	55	60		37.0	20.6	1.0364	1.0215	92	
	12	33			43.0	18.5	1.0330	1.0217	78	
	21	50			38.5	18.4	1.0335	1.0233	92	
	29	25			33.0	16.5	1.0323	1.0229	94	
	35	50			13.4	13.6	1.0301	1.0216	93	
	46	24			14.0	15.0	1.0324	1.0230	98	
Dog 52 Weight, 10.2 Kg	Control		245	153	11.5	27.0	1.0450	1.0286	105	52.1
	1	34	150		19.7	21.8	1.0392	1.0252	82	
	2	42		153	29.3	18.0	1.0335	1.0232	56	
	4	47	50		35.0	17.5	1.0325	1.0231	78	
	6	40			28.8	15.0	1.0311	1.0223	58	
	8	12			45.2	15.0	1.0313	1.0225	46	10.1
	9	9			42.9	14.8	1.0311	1.0224	60	
	12	9			37.0	13.7	1.0310	1.0226	55	
	22	25			51.7	12.5	1.0307	1.0230	56	
	28	12			56.0	12.0	1.0296	1.0227	60	
	34	22			46.8	10.5	1.0299	1.0231	63	
	45	59			47.6	10.8	1.0310	1.0241	67	
	47	9			46.5	11.0	1.0304	1.0238		7.0
	48	9			47.2	10.8	1.0306	1.0240	76	
	52	37			38.5	10.5	1.0303	1.0242	79	
	58	44			22.5	10.5	1.0307	1.0233	90	
	68	29			18.2	10.0	1.0304	1.0241	92	15.7
	69	32			16.1	10.0	1.0303	1.0242		
	70	29			16.2	10.0	1.0300	1.0242		
	125	27			17.1	10.2	1.0322	1.0259	98	
	126	40			17.5	10.2	1.0318	1.0258		24.4
	148	11			20.3	10.5	1.0313	1.0259	110	
	149	36			21.0	10.5	1.0316	1.0259		20.0

TABLE 5—*Effects of a Combination of Feeding Blood and Low Blood Pressure (Produced by Bleeding) on Blood Urea Nitrogen Levels—Continued*

	Interval After First Bleeding		Bled, Cc	Fed Blood, Cc	Blood Urea Nitrogen, Mg /100 Cc	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm Hg	Urea Clearance, Cc /Min
	Hr	Min					Blood	Plasma		
Dog 54 Weight, 7.8 Kg										
	Control		190	117	7.0	36.4	1.0502	1.0260	136	49.5
		47	117		8.5	30.0	1.0439	1.0228	120	
	2	15		117	12.3	24.5	1.0384	1.0221	63	
	3	16	75		13.3	24.0	1.0383	1.0221	72	
	4	57			17.3	20.5	1.0336	1.0201	65	
	6	59	40		19.3	18.4	1.0324	1.0200	75	
	8	30			28.0	16.0	1.0301	1.0194	58	3.2
	9	40			22.8	16.0	1.0307	1.0199	56	
	12	7			27.9	15.3	1.0319	1.0203	54	
Dog 56 Weight, 8.0 Kg										
	Control		190	120	6.6	39.4	1.0519	1.0237	138	36.1
	1		130		9.7	35.0	1.0486	1.0219	100	
	1	50	50	120	13.0	34.8	1.0467	1.0215	80	
	3	8	40		18.9	33.0	1.0447	1.0210	78	
	5	21	10		28.4	28.5	1.0428	1.0208	72	
	6	59	40		25.2	24.8	1.0377	1.0196	70	
	8	39			30.8	23.5	1.0355	1.0199	67	17.4
	9	43			32.2	22.2	1.0354	1.0196	64	
	12	18			31.2	20.1	1.0329	1.0196	69	
	22	57			11.2	17.0	1.0324	1.0204	90	
	28	36			8.1	16.8	1.0321	1.0208	100	
	29	47			4.9	15.6	1.0312	1.0204		49.4
	51	50			2.4	15.2	1.0323	1.0215	112	
	52	46			3.4	14.6	1.0321	1.0217		57.5
Dog 59 Weight, 10 Kg										
	Control		240	170	10.5	32.0	1.0614	1.0254	165	36.5
	1	20	60	150	12.2	42.3	1.0534	1.0227	116	
	2	49	100		14.6	42.5	1.0519	1.0222	82	
	4	47	100		24.4	47.5	1.0479	1.0211	79	
	7	30			30.8	30.0	1.0445	1.0205	27	
	8	53			38.2	33.0	1.0450	1.0212	17	
	9	5	Died							
Dog 61 Weight, 5.8 Kg										
	Control		140	87	11.3	45.3	1.0559	1.0242	117	41.1
	1	4	98		14.0	35.0	1.0479	1.0206	121	
	2	22	75	87	19.6	36.5	1.0479	1.0202	84	
	3	53			26.9	30.0	1.0427	1.0187	52	
	4	53	25		31.7	26.7	1.0389	1.0177	68	
	6	36			39.4	23.7	1.0352	1.0172	55	
	7	47			47.5	22.8	1.0384	1.0177	54	
	9	3			54.6	21.8	1.0348	1.0178	56	6.2
	10	11			51.7	22.0	1.0346	1.0182	55	
	12	17			51.3	21.0	1.0345	1.0186	53	
	22	37			20.3	18.0	1.0333	1.0195	81	
	24	20			11.8	17.5	1.0321	1.0193	78	
	28	22			11.2	16.5	1.0321	1.0194		31.3
	29	32			10.0	15.8	1.0315	1.0195	75	
	47	39			11.8	14.0	1.0316	1.0215	84	
	48	42			11.8	13.2	1.0316	1.0214		26.5

Determinations of blood pressure were made on dogs 58, 60 and 62. It will be noted that the pressures remained normal throughout the experiment. The elevation of blood urea nitrogen was in no way therefore due to lowering of the blood pressure by the absorption from the intestine of a vasodilating substance produced by the digestion of blood.

Studies of urea clearance were also made on dogs 58, 60 and 62. The values were at all times normal and therefore indicate that the elevation of blood urea nitrogen due to blood in the intestine is not caused by the absorption from the intestine of a nephrotoxic substance which decreases renal function.

III Effect on the blood urea nitrogen of a lowered blood pressure due to bleeding

Table 4 contains the data obtained from the study of 7 dogs, on 3 of which studies of urea clearance were made. Water was withheld for the first twelve to twenty-four hours of the experiment. The data show that there may be an extensive elevation of the urea nitrogen levels following bleeding. The following conclusions seem justified. While there is a very slight rise in the urea nitrogen values regardless of the effects on the blood pressure, the rise in urea nitrogen is not beyond the normal range unless the systolic blood pressure is lowered to less than 80 mm. The slight rise in blood urea

nitrogen in most of the dogs in this group before the systolic pressure was reduced to below 80 mm may have been due to the handling of the dogs and is probably an insignificant normal variation, but most probably it was due to the fact that blood pressures were taken and if found not down to significantly low levels the animal was bled. The pressures were not taken at the end of the bleeding but at approximately two hour intervals after the previous bleeding. It seems likely that the pressure was down for a period after each bleeding but may have come back before the next reading of pressure was taken.

When the pressures are reduced to 80 mm or below and maintained there, a characteristic curve results. The blood urea nitrogen goes up slowly, reaches a peak in twelve to twenty-four hours and slowly falls. This is in contradistinction to the quicker rise and fall seen when blood is given by stomach tube.

Studies on dogs 53, 55 and 57 show that there is a great reduction in renal function coincidental with the peak elevation of blood urea nitrogen and with the greatest reduction in blood pressure. With return of the blood pressure to normal levels, the urea clearance increases toward or to normal values.

The hematocrit values and specific gravity of blood and plasma in this group of dogs show progressively the changes characteristic of those which follow hemorrhage. No type of fluid shift which would confuse the interpretations is manifested by these results.

It is concluded from the study of the data obtained from this group of dogs that the loss of blood alone may result in elevation of the blood urea nitrogen if the loss of blood sufficiently lowers the blood pressure. In this group of dogs the critical level of pressure appears to be about 80 mm of mercury systolic.

We interpret the data to indicate that the elevation of urea nitrogen associated with the external loss of blood is due to diminished renal function which results from lowering the blood pressure.

IV Effect on the blood urea nitrogen of a combination of lowering the blood pressure by bleeding and feeding of blood

Eleven dogs were studied in this group. On 5 of the 11 studies of urea clearance were made. In general, the combination of procedures (bleeding and feeding blood) results in the early rise of urea nitrogen characteristic of feeding blood, the prolonged rise characteristic of lowered pressure and a greater rise than is characteristic of either procedure alone. In general also it is seen that

the systolic blood pressure must be reduced below the critical level of about 80 mm of mercury to produce decided and prolonged rises in blood urea nitrogen. It may also be noted that the peak values for the blood urea nitrogen coincided usually with the greatest fall in blood pressure, and the lowest values for urea clearance coincided with both.

TABLE 6—*Effect of Severe Anemia on Urea Nitrogen After Feeding of 30 Cc/Kg of Whole Blood*

	Interval After First Bleeding		Blood Fed, Cc	Blood Urea Nitrogen, Mg per 100 Cc	Hema- tocrit, %	Specific Gravity	
	Hr	Min				Blood	Plasma
Dog 23							
Weight, 9.8 Kg							
Control			147	17.5	23.3	1.0419	1.0267
2	23		147,	24.5	22.8	1.0432	1.0269
4	6			30.8	23.7	1.0424	1.0263
6	2			4.5	24.8	1.0424	1.0267
9	12			35.0	23.9	1.0413	1.0267
12	33			27.3	22.8	1.0419	1.0273
21	46			21.0	25.2	1.0445	1.0277
25	18			19.0	23.0	1.0421	1.0271
32	53			17.5	23.1	1.0417	1.0268
48	19			17.5	24.0	1.0424	1.0269
Dog 24							
Weight, 13.5 Kg							
Control			202	8.4	21.8	1.0392	1.0242
2	25		202	16.8	24.3	1.0409	1.0248
4				26.5	22.8	1.0402	1.0250
5	55			30.8	22.5	1.0397	1.0256
9	5			21.0	21.3	1.0389	1.0253
12	26			17.5	20.8	1.0387	1.0248
21	40			14.0	22.0	1.0401	1.0249
25	11			15.3	24.4	1.0384	1.0249
35	52			8.4	23.8	1.0398	1.0249
48	12			5.6	24.0	1.0409	1.0249
Dog 25							
Weight, 13.4 Kg							
Control			201	18.2	26.5	1.0421	1.0229
2	22		201	22.5	22.8	1.0389	1.0218
3	54			28.0	22.6	1.0379	1.0215
5	51			33.0	25.9	1.0419	1.0233
9				23.0	26.2	1.0421	1.0233
12	20			18.2	25.3	1.0410	1.0223
21	34			14.0	26.8	1.0427	1.0228
25	5			14.0	22.9	1.0394	1.0223
32	46			10.5	21.8	1.0373	1.0215
48	7			8.4	22.1	1.0386	1.0221
Dog 26							
Weight, 12.4 Kg							
Control			186	25.0	25.5	1.0429	1.0249
2	22		186	28.7	25.9	1.0441	1.0256
3	50			37.0	26.9	1.0448	1.0259
5	47			45.0	24.5	1.0417	1.0248
8	54			30.0	22.0	1.0392	1.0238
12	13			22.4	22.3	1.0400	1.0238
21	29			21.0	23.6	1.0411	1.0240
24	59			21.8	19.7	1.0376	1.0231
32	40			14.6	21.7	1.0381	1.0233
48	1			10.5	20.6	1.0376	1.0225

V Effect on the blood urea nitrogen of anemia due to bleeding

It may be ascertained from a study of the data in tables 4 and 5 that anemia itself, even of severe grades, is not sufficient to cause elevation of the blood urea nitrogen. For example, dog 57 (table 4) had a blood urea nitrogen level of

96 mg per hundred cubic centimeters with a hematocrit value of 114 per cent. Similarly dog 30 (table 5) had a value for blood urea nitrogen of 93 mg per hundred cubic centimeters and a hematocrit value of 13 per cent. Many other dogs mentioned in tables 4 and 5 showed similar relationships, but these 2 exemplify the point better. Dog 63 (table 7) also

TABLE 7—*Effect of Severe Anemia on Renal Function as Measured by Urea Clearance*

Interval After First Bleeding, Days	Bled, Cc *	Blood Urea Nitrogen, Mg per 100 Cc	Hema- tocrit, %	Specific Gravity		Blood Pres- sure, Mg Hg	Urea Clear- ance, Cc per Min
				Blood	Plasma		
Dog 63							
Weight, 5.8 Kg							
Control	358	11.3	45.3	1.0559	1.0242	117	41.1
2		11.8	13.2	1.0316	1.0214	84	26.5
7		8.2	16.2	1.0333	1.0224	91	32.0
Dog 64							
Weight, 7.2 Kg							
Control	365	14.5	42.5	1.0577	1.0292	146	38.9
3	150		19.1	1.0377	1.0255	112	
4	50		13.7	1.0322	1.0231	108	
7		9.3	15.6	1.0353	1.0263	120	29.7
Dog 65							
Weight, 7.7 Kg							
Control		13.3	46.4	1.0553	1.0233	132	36.8
2	250	6.4	38.1	1.0497	1.0227	116	42.8
20	350	14.6	28.0	1.0434	1.0237		35.7
23	110		15.4	1.0317	1.0228	100	
24	40		13.4	1.0308	1.0229	90	
27	242	19.7	13.0	1.0330	1.0254	100	27.1
(261 cc of plasma returned)							
31			9.0	1.0311	1.0254	89	18.7
Dog 66							
Weight, 9.0 Kg							
Control	436	10.5	37.2	1.0488	1.0227	121	41.1
2		10.1	12.0	1.0286	1.0206	96	27.4
20		12.5	12.5	1.0300	1.0238	105	16.4
23			12.4	1.0303	1.0261	110	
24			13.8	1.0321	1.0258	100	
27		29.9	15.0	1.0338	1.0279	86	25.8
28	Died						
Dog 67							
Weight, 4.6 Kg							
Control		5.7	33.9	1.0559	1.0236	129	67.2
2		6.3	26.3	1.0422	1.0218	119	79.2
7		8.2	30.3	1.0439	1.0215	138	37.8
8	250						
10	220		18.4	1.0333	1.0210	120	
11	158		13.6	1.0300	1.0206	128	
14		12.6	13.2	1.0318	1.0240	110	24.6
Died							

* Bled by puncture of the jugular vein after determinations were made

clearly showed that even severe anemia does not suffice to cause an elevation of blood urea nitrogen.

VI Effect on the blood urea nitrogen of giving anemic dogs 30 cc per kilogram of whole blood and of anemia on renal function as measured by urea clearances

Table 6 contains the data pertaining to our study of the combined effects of feeding blood and anemia on the blood urea nitrogen. Four

dogs made anemic by previous bleeding, usually a number of days before, served as the subjects of this phase of the experiment.

Comparison of the data in table 6 and table 3 shows that there is no greater rise in the blood urea nitrogen produced by giving 30 cc of blood per kilogram to anemic dogs than results from giving blood to dogs with normal hematocrit values. Hematocrit levels of about 50 per cent of the normal were present in several instances.

Table 7 contains the data for 5 dogs on which the effect of anemia on the urea clearances were studied. Urea clearances were determined on dogs with normal or slightly low hematocrit levels. By bleeding these animals, the hematocrit values were gradually reduced, in some instances to rather low levels, and the urea clearance was determined at intervals as the hematocrit levels were reduced by repeated bleedings.

Analysis of the data presented in tables 6 and 7 does not result in an entirely clear concept concerning the effect of anemia on urea clearance. The data, however, appear to warrant the following conclusions. Moderate decrease in the hematocrit values is not associated with a decrease in urea clearance. While severe anemia is associated with a decrease in the urea clearance as compared with the control level obtained when hematocrit values are normal, this decreased level may still be well within the range of normal for dogs in general. In some instances (dog 65) the striking decrease was also associated with a low blood pressure. While there appears to be a definite decrease in urea clearance as a result of a severe anemia, this anemia alone is never the cause of an elevated blood urea nitrogen level.

VII Effect of forcing of water on the urea nitrogen level following ingestion of 30 cc of blood per kilogram in two equal doses

Comparison of the results in table 8 with those recorded in table 3 will show that the giving of 10 cc of water per kilogram by tube to 2 dogs and as much as 50 cc per kilogram of water by tube to 1 dog did not affect the level to which the blood urea nitrogen rises after the giving of blood by stomach tube. Neither did it affect the rate at which the peak is reached, nor did it alter the time required for the blood levels of urea nitrogen to return to normal.

As in all our other experiments, the hematocrit values and the specific gravity of the blood and plasma indicated no fluid shifts which could confuse the results.

It is concluded from a limited number (3) of experiments that forcing of water in doses

of 10 to 50 cc per kilogram does not affect the level to which the blood urea nitrogen rises as a result of blood given in doses of 30 cc per kilogram by stomach tube

VIII Effect of forcing water on the elevation of blood urea nitrogen associated with the low blood pressure caused by hemorrhage

Comparison of the levels of blood urea nitrogen in table 4 with those in table 9 in dogs bled

to remain higher at comparable blood pressures in the group given water

Chart 1 presents these comparisons graphically. It can be noted from analysis of the curves that the blood pressures in the two groups are comparable and that not only do the levels of urea nitrogen fail to go as high in the dogs given water but they fall to normal a number of hours before they do in those dogs for which water was restricted for twenty-four hours

In order to throw further light on the mechanisms involved, the blood urea nitrogen levels in the group given water and in the group not given water were correlated with the changes in the specific gravity of the blood and plasma

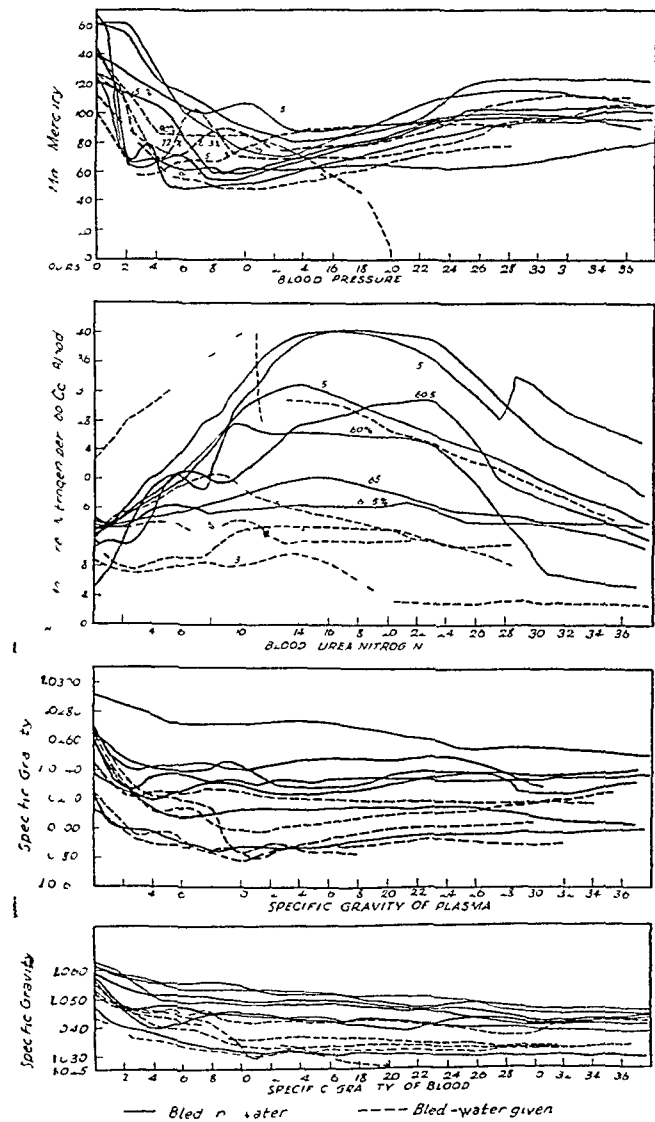


Chart 1—Comparison of blood pressures, blood urea nitrogen levels and specific gravities of the blood and of the plasma of dogs which were bled and given water in the first twenty-four hours (broken lines) and of dogs bled and not given water (solid lines). Percentages in the upper graphs indicate the percentage of the total calculated blood volume removed

to reduce the blood pressure to comparable levels in both groups shows that the levels of blood urea nitrogen are definitely lower in the dogs bled and given water by tube than those of a group of dogs treated similarly except that water was restricted for the first twenty-four hours. It will be seen also that the urea clearance tends

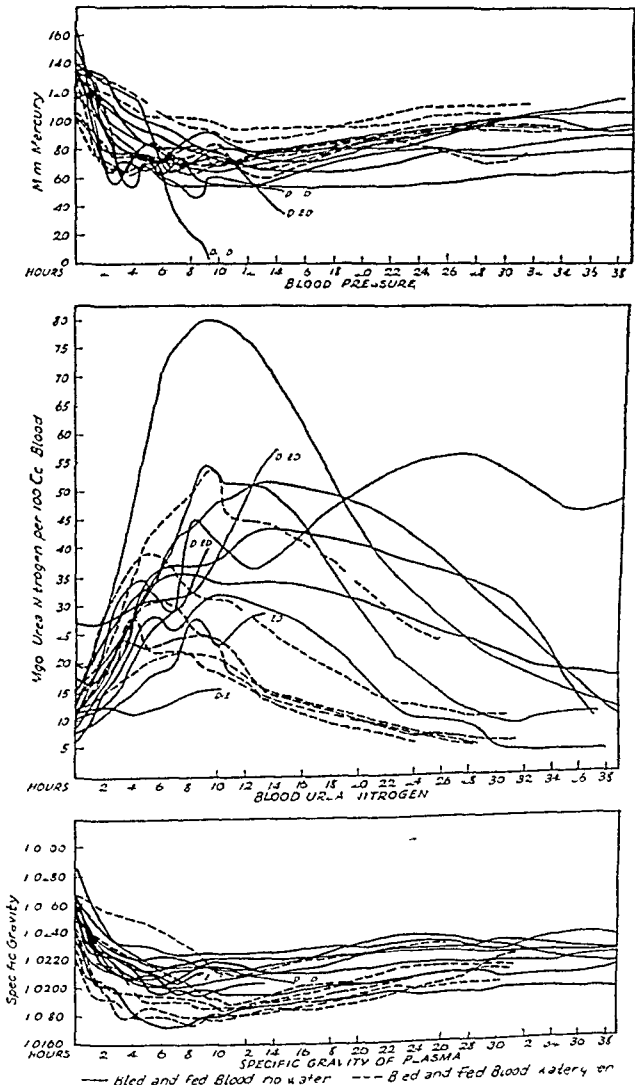


Chart 2—Comparison of blood pressures, blood urea nitrogen levels and specific gravities of the plasma of dogs bled and fed blood to which water was given (broken lines) and of dogs to which water was not given (solid lines) in the first twenty-four hours

It appears warranted to say that the blood urea nitrogen levels rise to significantly lower levels when the animals are given water. This

may be due to increased dilution of all body fluids or to better renal excretion

IX Effect of forcing of water on the elevation of blood urea nitrogen due to a combination of low blood pressure and feeding of blood

Comparison of the results recorded in tables 5 and 10 show definitely that the level to which the blood urea nitrogen rises in dogs as a result

In general, the values for urea clearance in the two groups were higher in the group given water by stomach tube than they were in the group in which water was restricted. It is likely, then, that the giving of water was beneficial even when comparable blood pressures were obtained

Chart 2 shows these comparisons more effectively graphically than do tables 5 and 10

TABLE 8—*Effect of Water by Stomach Tube on Urea Nitrogen After Feeding of 30 Cc/Kg of Blood by Stomach Tube*

Dog 38 Weight, 11.6 Kg	Interval After First Bleeding		Water Given, Cc	Fed Blood, Cc	Blood Urea Nitrogen, Mg /100 Cc	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm Hg	Urea Clearance, Cc /Min
	Hr	Min					Blood	Plasma		
	Control		116	174	8.4	40.0	1.0533	1.0267	117	104.0
	2	15		174	15.4	42.0	1.0533	1.0264		
	4	20			23.2	39.8	1.0526	1.0261	124	
	6	7			34.4	39.0	1.0520	1.0253		
	7	8			28.0	39.0	1.0498	1.0262		76.0
	8	9			23.8	36.0	1.0493	1.0259		
	12	8			11.2	34.0	1.0460	1.0252		
	19	50			4.2	37.0	1.0489	1.0263		
	27	13			4.8	35.0	1.0489	1.0253		55.0
	31	20			4.4	31.0	1.0474	1.0246		
	43	25			2.1	35.0	1.0509	1.0255		
Dog 42 Weight, 9.8 Kg	Control		463	140	8.4	37.5	1.0516	1.0272		58.4
	2	28		140	21.0	36.0	1.0519	1.0276		
	4	7	465		30.0	35.0	1.0523	1.0280		
	5	15			32.9	37.0	1.0517	1.0280		
	6	22			30.8	35.0	1.0488	1.0262		92.8
	7	23			25.5	35.0	1.0496	1.0267		
	8	27			23.1	33.5	1.0486	1.0267		
	14	9			11.9	35.0	1.0506	1.0276		
	22	5			9.1	38.0	1.0528	1.0282		
	28	45			9.1	38.5	1.0526	1.0282		
	35	18			10.0	37.5	1.0524	1.0278		
	46	5			12.4	39.5	1.0533	1.0279		
Dog 40 Weight, 14.5 Kg	Control		145	218	34.0	43.7	1.0545	1.0245		36.2
	2	10		210	36.4	42.0	1.0540	1.0238		
	4	10			48.2	40.0	1.0540	1.0242		
	5	42			51.7	42.0	1.0537	1.0243		
	6	50			51.7	41.0	1.0528	1.0244		46.2
	7	40			35.3	39.8	1.0519	1.0232		
	9	15			28.3	38.0	1.0410	1.0228		
	12	40			18.9	34.4	1.0487	1.0225		
	20	20			13.3	39.0	1.0524	1.0240		
	27	8			18.9	39.6	1.0507	1.0242		
	35	10			20.0	44.0	1.0567	1.0244		
	44	40			18.2	42.0	1.0542	1.0237		

of low blood pressure and feeding of blood is significantly less when water is given by stomach tube than when water is restricted. Study of the detailed figures for specific gravity of plasma in the two groups (with and without water) appears to show that there is no significant difference. It seems unlikely, therefore, that the lower levels of urea nitrogen in the group given water is due to a dilution effect of the plasma.

It is concluded therefore that dehydration may be a factor in the extent to which blood urea nitrogen values rise as a result of feeding blood and of low blood pressures.

SUMMARY AND CONCLUSIONS

Azotemia associated with gastrointestinal hemorrhage was investigated by estimating the effects on the blood urea nitrogen of lowering

TABLE 9—*Effect of Water by Stomach Tube on the Blood Urea Nitrogen in Dogs with Low Blood Pressure from Hemorrhage*

	Interval After First Bleeding		Water Given, Cc	Bled, Cc	Blood Urea Nitrogen, Mg /100 Cc	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm Hg	Urea Clearance, Cc /Min
	Hr	Min					Blood	Plasma		
Dog 37 Weight, 11.1 Kg			111							
	Control			275	9.1	43.5	1.0542	1.0271	110	54.0
	2	5		174	7.4	34.8	1.0452	1.0236	88	
	5	10		50	8.1	36.0	1.0463	1.0225	71	
	6	27			8.4	36.0	1.0448	1.0223		
	7	28			8.8	36.0	1.0457	1.0238	86	101.0
	8	29		100	8.1	36.0	1.0439	1.0228	89	
	12	15			9.8	34.0	1.0420	1.0221	74	
	20	10		(67.3%)*	3.5	31.0	1.0403	1.0219	81	
	27				3.5	23.0	1.0352	1.0219	104	82.0
	31	45			3.2	23.0	1.0397	1.0218	110	
	43	50			3.2	23.5	1.0399	1.0229	96	
Dog 39 Weight, 10.5 Kg			105							
	Control			250	22.4	44.7	1.0544	1.0268	126	15.5
	2			175	28.0	34.0	1.0459	1.0233	105	
	4	3		50	30.8	27.0	1.0403	1.0212	65	
	6	30		90	35.6	28.0	1.0399	1.0215	104	
	9	9		42	38.4	21.4	1.0339	1.0199	72	
	10	35			42.0	21.1	1.0325	1.0198		
	11	41		(72%)*	27.0	19.5	1.0319	1.0199		4.2
	12	40			29.4	19.5	1.0324	1.0201	68	
	20	15			26.6	19.0	1.0327	1.0211	70	
	27	10			21.3	19.0	1.0314	1.0217	92	
	35	3			14.7	15.0	1.0317	1.0226	102	
	44	35			11.9	15.0	1.0338	1.0238	100	
Dog 41 Weight, 9.7 Kg			485							
	Control			250	14.0	42.0	1.0525	1.0246	140	22.9
	1	58		165	13.3	37.5	1.0475	1.0227	116	
	3	59		100	14.0	35.5	1.0456	1.0224	86	
	7	41	485	85	12.6	31.5	1.0421	1.0216	86	
	9	50	485	100	14.7	22.5	1.0328	1.0183		
	10	43			14.0	21.0	1.0296	1.0160		
	11	50		(90%)*	12.6	26.0	1.0332	1.0189	78	33.1
	12	47			11.2	26.0	1.0332	1.0189		
	14	10			11.9	23.5	1.0312	1.0165	62	
	20		Died							
Dog 47 Weight, 8.2 Kg			82 82							
	Control			200	12.4	31.0	1.0433	1.0212	100	35.0
	1	18		130	13.6	26.0	1.0403	1.0203	84	
	2	37			15.6	25.5	1.0361	1.0194	58	
	4	7			17.0	24.0	1.0355	1.0190	59	
	5	34	82	40	19.1	23.0	1.0346	1.0189	66	
	7	44			20.1	20.0	1.0329	1.0186	65	
	8	54	82	(56.4%)*	20.4	20.0	1.0315	1.0188		30.3
	9	56			18.8	19.0	1.0306	1.0183	75	
	12	15			16.4	17.0	1.0306	1.0187	85	
	21	39			12.0	17.8	1.0310	1.0200	90	
	27	57			11.0	16.0	1.0318	1.0203	90	
Dog 49 Weight, 6.3 Kg			63 63							
	Control			150	11.7	39.0	1.0509	1.0225	125	9.0
	1	10		100	8.4	38.0	1.0491	1.0212	120	
	2	35		75	7.5	36.0	1.0455	1.0198	83	
	4	45			8.9	33.0	1.0437	1.0197	58	
	6	8	75		9.1	31.8	1.0415	1.0190	56	
	7	37		75	9.1	30.0	1.0404	1.0186	83	
	8	55	75		11.9	29.0	1.0361	1.0181	49	9.1
	9	52		(79.4%)*	12.6	27.5	1.0351	1.0179	53	
	12	7			13.5	25.7	1.0354	1.0186	50	
	22	13			12.0	20.8	1.0330	1.0193	71	
	28	1			8.6	17.0	1.0312	1.0189	76	

* Total per cent of calculated blood volume removed

TABLE 10—*Effect of Feeding Water on Blood Urea Nitrogen of Dogs Bled and Fed Blood*

	Interval After First Bleeding		Water Given, Cc	Bled, Cc	Blood Fed, Cc	Blood Urea Nitrogen, Mg per 100 Cc	Hema- tocrit, per Cent	Specific Gravity		Blood Pressure, Mm Hg	Urea Clearance, Cc /Min
	Hr	Min						Blood	Plasma		
Dog 43 Weight, 9.5 Kg											
			95								
			95								
Control				200	143	10.8	36.5	1.0505	1.0266	130	25.4
2	8			150	143	18.9	32.0	1.0480	1.0255	120	
4	50		95	95		30.1	28.5	1.0441	1.0248	104	
8	25			100		25.7	21.8	1.0363	1.0226	102	
9	30					23.9	20.0	1.0343	1.0212		
10	30		95	(72.7%)*		18.1	19.5	1.0343	1.0213		
11	33					16.7	20.5	1.0333	1.0209	95	30.0
15	39					13.2	18.2	1.0335	1.0215		
23	20					6.3	17.6	1.0342	1.0228	102	
Dog 44 Weight, 13.6 Kg											
			136								
			136								
Control				280	204	15.6	42.0	1.0557	1.0243	132	39.9
2	2			200	204	22.5	40.0	1.0528	1.0231	128	
4	45		136	180		40.8	35.0	1.0479	1.0220	114	
8	26			145		51.2	28.5	1.0418	1.0200	95	
9	30		136			34.0	24.5	1.0366	1.0192		
10	25			(74%)*		46.6	24.5	1.0369	1.0191		
11	23					45.6	24.3	1.0355	1.0187	87	14.8
13	23					44.6	24.8	1.0365	1.0193		
23	7					27.3	21.8	1.0354	1.0204	109	
Dog 45 Weight, 5.9 Kg											
			59								
			59								
Control				150	89	14.8	46.0	1.0564	1.0241	138	28.5
1	1			100		17.2	41.5	1.0584	1.0210	128	
2	7			70	89	22.2	35.0	1.0445	1.0194	90	
3	4					24.5	31.0	1.0413	1.0179	62	
4	45		59	50		22.6	29.5	1.0404	1.0186	84	
8	18					25.0	24.5	1.0341	1.0178	68	
9	32		59	(78%)*		24.5	23.0	1.0333	1.0178		28.3
10	25					23.6	21.8	1.0325	1.0178	72	
12	42					16.1	20.0	1.0325	1.0183	66	
22	32					7.7	18.0	1.0335	1.0204	88	
29	15					5.6	16.5	1.0329	1.0215	95	
Dog 46 Weight, 8.0 Kg											
			80								
			80								
Control				200	120	19.8	36.0	1.0486	1.0229	128	34.4
0	52			130		19.2	32.0	1.0449	1.0208	100	
1	58			50	120	26.8	30.5	1.0414	1.0205	72	
2	41					32.0	28.0	1.0347	1.0199	66	
4	51		80	30		39.5	24.5	1.0363	1.0195	71	
8	8			50		32.4	20.4	1.0329	1.0192	83	
9	12			30		31.7	19.0	1.0317	1.0190	70	
10	9					31.7	Clot	1.0279	1.0184	68	
12	17			(76.5%)*		27.7	16.8	1.0280	1.0187	73	22.3
22	10					12.6	16.0	1.0309	1.0202	89	
28	50					10.1	15.0	1.0315	1.0209	92	
Dog 48 Weight, 7.3 Kg											
			73								
			73								
Control				175	110	17.5	35.0	1.0459	1.0221	106	26.7
1	19			75		15.8	24.4	1.0377	1.0193	77	
2	33			50	110	19.0	24.0	1.0339	1.0192	70	
3	57					27.8	20.0	1.0311	1.0181	66	
5	28		73	50		22.1	19.5	1.0311	1.0180	75	
7	41					22.4	16.5	1.0283	1.0175	64	
8	56		73	(60%)*		19.7	16.3	1.0284	1.0180		22.7
9	51					18.4	14.5	1.0272	1.0180	66	
12	6					15.1	13.5	1.0275	1.0181	76	
21	45					8.5	15.7	1.0292	1.0197	86	
27	47					5.5	14.0	1.0292	1.0198	76	
Dog 50 Weight, 7.2 Kg											
			72								
			72								
Control				175	108	11.9	35.3	1.0482	1.0243	106	10.8
1	10			115		13.5	28.0	1.0417	1.0220	96	
2	30			80	108	16.1	28.3	1.0404	1.0219	78	
4	47			50		19.7	20.0	1.0325	1.0192	74	
5	17		72			21.3	19.2	1.0316	1.0192	62	
7	39			50		22.2	18.0	1.0305	1.0190	74	
8	48		72			21.8	17.8	1.0291	1.0187		
9	47			(81.5%)*		21.6	17.0	1.0284	1.0186	83	7.0
12	2					17.2	15.0	1.0281	1.0187	59	
22	3					8.6	14.0	1.0299	1.0212	93	
27	49					5.5	13.0	1.0299	1.0214	96	

* Total per cent of calculated blood volume removed

blood pressure by bleeding, of feeding dog's blood by stomach tube, of anemia, of withholding water and of combinations of these in sixty-two experiments on dogs

Systolic blood pressures of 70 to 80 mm of mercury resulted in rises of blood urea nitrogen to 25 to 40 mg per hundred cubic centimeters. Blood by stomach tube raised the blood urea nitrogen levels to 25 to 30 mg per hundred cubic centimeters. The rise and fall of blood urea nitrogen due to ingested blood was faster than that due to low blood pressure. Severe anemia due to hemorrhage did not produce azotemia. Combined effects of low blood pressure and blood by stomach tube produced rapid rises of blood urea nitrogen characteristic of the latter, rises of longer duration characteristic of the former

and higher levels than one would expect from either alone

Urea clearance was not diminished in dogs given blood by stomach tube. Falls in urea clearance occurred in every dog in which there were a significant fall in blood pressure and an elevation of blood urea nitrogen. Values of urea clearance and blood urea nitrogen in dogs with different intakes of water indicate that dehydration may contribute to azotemia associated with gastrointestinal bleeding.

Azotemia associated with gastrointestinal bleeding may be due to decreased renal function caused by low blood pressure and dehydration or to absorption of digested blood proteins. Anemia is not a factor. Absorption of digested blood from the gastrointestinal tract does not decrease renal function.

APLASTIC ANEMIA AND ITS ASSOCIATION WITH HEMOCHROMATOSIS

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Although hemochromatosis is a comparatively rare condition, its association with aplastic anemia is frequent enough to suggest that the combination of the two diseases is more than accidental. The purpose of this paper is to draw further attention to this association by reviewing the reported cases, adding another case and discussing the pathologic changes common to the two conditions.

Whitby and Britton¹ stated that about 150 cases of idiopathic aplastic anemia are recorded in the literature on medicine. Thompson, Richter and Edsall² and later Rhoads and Miller³ drew attention to the discrepancy between the peripheral blood and the bone marrow and to the frequent occurrence of cellular and even hypercellular marrow when the elements in the peripheral blood were reduced in numbers. Rosenthal⁴ distinguished between two forms of aplastic anemia, the typical and the atypical. The atypical form includes the chronic type of aplastic anemia with cellular marrow, also called pseudoaplastic anemia. Bomford and Rhoads⁵ suggested that until a classification based on causation is available the term refractory anemia be used for every anemia which fails to respond to any form of treatment except trans-

fusions of blood. Israels and Wilkinson⁶ described the syndrome of achrestic anemia as different from aplastic anemia, but this separation has not been accepted by other investigators.⁷

In a study of 66 patients with refractory anemia, Bomford and Rhoads⁵ subdivided their cases into four groups according to the findings in the bone marrow. In 9 of 31 patients with refractory anemia characterized by partly mature cellular marrow, corresponding to the pseudoaplastic anemia described by other observers, a varying degree of pigmentation of the skin developed in the course of several years. In 3 patients with marked pigmentation, 1 of whom had diabetes, autopsy revealed the lesions of hemochromatosis. Kark⁸ and Mackey⁹ each reported an instance of chronic aplastic anemia complicated by hemochromatosis. No autopsy was done in Kark's case, so the diagnosis could not be confirmed except insofar as examination of a piece of excised skin showed changes that were said to be characteristic. The case of a patient with cirrhosis of the liver and pernicious anemia who after satisfactory response to liver therapy became hypersensitive to liver was reported by Markoff.¹⁰ Pigmentation of the skin developed, and the patient died because of anemia which was refractory to liver therapy and because of

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uncontrollable bleeding. The presence of hemochromatosis was confirmed at autopsy. However, studies of the bone marrow showed the changes of pernicious anemia, and for this reason the case is not included in our series. Other workers,¹¹ who reviewed larger numbers of cases of aplastic anemia, did not state that either pigmentation of the skin or hemochromatosis was revealed at autopsy.

Sheldon,¹² in his monograph reviewing the literature on hemochromatosis up to 1935, stated that "the blood picture is normal except for a slight degree of anemia which is by no means constant, and is no more than is to be expected in the terminal stages of any chronic disease." Naegeli¹³ mentioned the occasional occurrence of anemia in hemochromatosis. Butt and Wilder¹⁴ described the cases of 30 patients for whom a diagnosis of hemochromatosis was made during life. These authors found an average of 3,990,000 red blood cells per cubic millimeter with slight macrocytosis in 3 patients. Wintrobe and Shumacker's and Wintrobe's papers¹⁵ mentioned 1 case of their own and 4 in the literature in which pigmentary cirrhosis was present with macrocytic anemia. A case of pernicious anemia associated with hemochromatosis was reported by Roth¹⁶ and by Cain.¹⁷ R. R. Kiacke, discussing Cain's paper,¹⁷ mentioned a patient with macrocytic anemia, hepatomegaly and splenomegaly, without glycosuria and without abnormal pigmentation of the skin, who at autopsy presented the visceral changes of hemochromatosis. No further details of the autopsy or of the blood picture were given. In Meader's

case¹⁸ immature forms of erythrocytes and granulocytes were present in the peripheral blood. Even from this short review it is apparent that anemia is not a feature of hemochromatosis and that if present it is due to complicating conditions.

REPORT OF A CASE

P. B., a 65 year old white American of German extraction, was admitted to Goldwater Memorial Hospital on Sept. 22, 1943. He complained of weakness, shortness of breath and swelling of the legs.

History—The patient had been a structural engineer until 1929. Since then he had worked as a laborer. There was no available evidence of exposure to hemotoxic agents. He had consumed large amounts of alcohol in his youth, but his intake for the past thirty years had been moderate. None of his family was known to have suffered from any disease of the blood. There was nothing in his history which could be considered relevant to his present condition.

Approximately five years prior to the patient's first admission to the hospital his marked pallor had been commented on by his wife and his friends, but he felt well and did not seek medical attention. In December 1942, weakness, dyspnea on exertion and edema of the region of the ankles necessitated hospitalization. During the following seven months he was readmitted to the hospital five times for blood transfusions. In April 1943 he was readmitted because of congestive heart failure and was given maintenance doses of digitalis and mercurial diuretics.

The patient stated that he had lost 30 pounds (13.6 Kg.) since 1940. There was no history of dyspepsia, burning of the tongue, dysphagia, tendency to bleed or to bruise easily or paresthesias. He was hospitalized in another institution from July to September 1943, when he was transferred to Goldwater Memorial Hospital. Treatment in both hospitals consisted of intramuscular administration of large quantities of liver extract, iron and vitamins and transfusions of blood.

Physical Examination—At the time of his admission to the hospital the patient appeared well developed but chronically ill. He was not dyspneic. There was evidence of recent loss of weight. The skin and the visible mucous membranes were strikingly pale, with a suggestion of an icteric tint. On the left forearm two ecchymoses, approximately 1 cm. in diameter, were present, and many irregularly shaped dark brown-pigmented areas were visible over the dorsa of the hands and on the forearms. No other signs of pigmentation were noted. There were no detectable enlargements of the lymph nodes. The eyelids were slightly edematous. The scleras were lemon yellow. The fundi were not pale. There were old small retinal hemorrhages in the right eye. Slight atrophy of the lateral borders of the tongue was noted. Engorgement of the veins of the neck was observed, and arterial pulsations were seen in the supraclavicular spaces. There were a few moist rales over the base of each lung. The heart was enlarged to the left. The sounds were of good quality, with a soft systolic murmur at the apex transmitted toward the base. The blood pressure was 150 mm. of mercury systolic and 50 diastolic. The liver was palpable 9 cm. below the costal margin in the midclavicular line, it was firm and nontender, and the edge was sharp. The spleen was palpable 2 cm. below the left costal

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margin and was firm and not tender. No fluid wave or shifting dullness was present. The genitalia were normal except for edema of the scrotum. There was pitting edema of the lower extremities. Koilonychia was not seen. The reflexes were normal. There were no sensory disturbances, and the senses of vibration and position were normal.

Laboratory Data—Urine The urine was concentrated to 1024. It gave negative reactions to tests for albumin and sugar and (in a dilution of 1:10) to the test for urobilinogen. Tests for bile and for Bence Jones protein also gave negative results. Examination of the urinary sediment revealed no abnormal changes. The results of the phenolsulfonphthalein test were as follows: first hour, excretion of 30 per cent of the dye; second hour, excretion of 10 per cent.

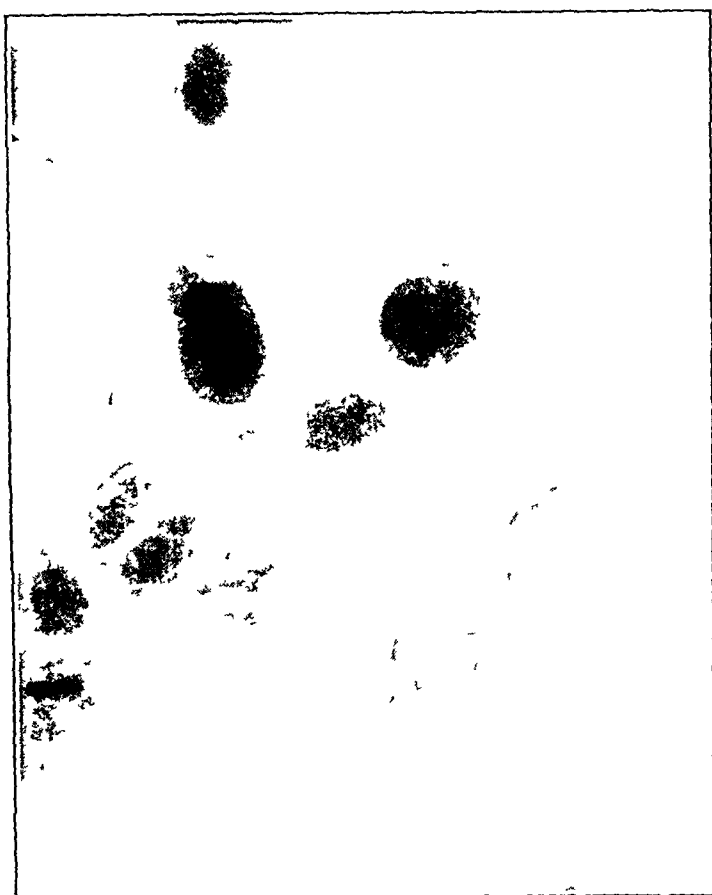


Fig. 1—Smear of sternal marrow showing normoblasts in different stages of development. The cell in the lower left corner represents the earliest normoblast in the field. The cell placed next to it for comparison is a myelocyte. The cell below the myelocyte is a pronormoblast. Wright's stain, $\times 1,600$.

Blood The fasting level of the blood sugar on two occasions was 110 mg and 130 mg respectively per hundred cubic centimeters. The dextrose tolerance test showed a fasting level of 118 mg per hundred cubic centimeters of blood, one hour after administration of 100 Gm of dextrose, 214 mg, and two hours after administration of dextrose, 167 mg. (Dextrose was absent from the urine throughout this test.) The blood contained 34 mg of nonprotein nitrogen per hundred cubic centimeters. It showed 4.3 mg of uric acid, 8.9 mg of calcium and 4.6 mg of phosphorus per hundred cubic centimeters. The serum contained 1.4 Bodansky units of alkaline phosphatase and 114 mg of cholesterol (51.4 mg as esters) per hundred cubic centimeters. The total protein was 5.6 Gm, the albumin 3.98 Gm and the globulin 1.69 Gm, per hundred cubic centimeters. The

sulfobromophthalein sodium test (5 mg, per kilogram of body weight) showed retention of 75 per cent of the dye after thirty minutes and no retention after forty-five minutes. The cephalin flocculation test gave negative results. The prothrombin time, determined with diluted plasma (12.5 per cent), was seventy seconds (normal, thirty-seven to forty-two seconds). With daily parenteral administration of 6 mg of menadione in corn oil the prothrombin time decreased to sixty-one seconds on the sixth and seventh days and increased to seventy-five seconds on the ninth and tenth days. In the congo red test 77.4 per cent of the dye was left in the blood after one hour. The icterus index was 4.5 and 4 units. The van den Bergh direct test gave negative results, the indirect showed a slight trace of bilirubin. The Kahn and Kline reactions of the blood were negative.

On the patient's admission to the hospital there were 1,400,000 red blood cells, 4,900 white blood cells and 216,000 platelets per cubic millimeter, the hemoglobin content was 36 per cent and the reticulocytes amounted to 3.1 per cent. The mean corpuscular volume was 100 cubic microns, the mean corpuscular hemoglobin 33 micromicrograms and the mean corpuscular hemoglobin content 33 per cent. The color index was 1.1. The differential count was as follows: polymorphonuclear cells 48 per cent, stab cells 14 per cent, eosinophils 2 per cent, basophils 1 per cent, monocytes 3 per cent and lymphocytes 32 per cent. The red cells showed marked anisocytosis and poikilocytosis. Many macrocytes were seen. Polychromatophilic and large basophilic stippled red cells were rare. Two normoblasts per hundred white blood cells were counted. The bleeding time, the coagulation time and the reaction to the Rumpel-Leeds test were normal. The result of a test of the red cells for fragility gave results within normal limits.

During the patient's stay in the hospital his red cell counts varied between 1,150,000 and 2,500,000, his hemoglobin between 34 per cent and 54 per cent and his white blood counts between 2,600 and 6,100. The reticulocyte count decreased to below 1 per cent during the last two months.

Bone Marrow An aspiration of the bone marrow was done on Oct. 27, 1943. The smears were very cellular. There was an increase in the percentage of nucleated red cells, with basophilic and polychromatic normoblasts predominating (fig. 1). The number of mature granulocytes was markedly diminished. Hemosiderin was present in the reticulum cells, the number of which was increased.

The following tabulation summarizes the differential count of the cells of the bone marrow.

	Per Cent		Per Cent
Myeloblasts	2.0	Polymorphonuclear cells, neutrophilic	1.8
Promyelocytes	2.2	Lymphocytes	4.8
Myelocytes		Reticulum cells	3.4
Neutrophilic	4.6	Undifferentiated cells	0.6
Eosinophilic	0.6	Pronormoblasts	2.0
Metamyelocytes		Normoblasts	
Neutrophilic	6.2	Basophilic	18.2
Eosinophilic	0.6	Polychromatic	26.0
Stab forms		Orthochromatic	8.8
Neutrophilic	18.0		
Eosinophilic	0.2		

Stomach On gastric analysis free hydrochloric acid was found in a fasting specimen and in all specimens after administration of alcohol.

Stool No ova, parasites or occult blood were demonstrated in the stool.

Roentgen Findings (Reported by Dr Henry K Taylor)—The lungs were normal except for a moderate degree of emphysema. The heart was enlarged, and the configuration was of a hypertensive type.

There was no increase in the density of the liver.

There was no evidence of osteosclerosis of the skull, spine, pelvis or lower extremities. The middle third of the tibiae showed an increase in the thickness of the cortex, with no encroachment on the medullary canals. The lumbar portion of the spine showed productive changes in the bone. The cranial vault was normal in thickness. The diploic layer was barely perceptible. The density of the vault was probably greater than the average, but was insufficient to be considered evidence of osteosclerosis. There were calcific deposits in the choroid plexus. The sella turcica showed nothing abnormal. There were irregular areas of calcification in the pituitary fossa.

Roentgenograms of the skull, the femurs and the alimentary canal made at another hospital revealed no additional information, the calcific deposits in the choroid plexus and in the pituitary fossa were noted also.

In view of the large amounts of iron pigment found in the various organs at autopsy, it is possible that the radiopaque densities considered as calcific deposits in the choroid plexus and in the pituitary fossa were due to incrustations of iron. However, since permission for necropsy did not include the brain, this hypothesis could not be confirmed.

Electrocardiographic Findings—The electrocardiogram showed normal sinus rhythm with occasional premature auricular contractions. There was deviation of the electrical axis to the left and left bundle branch block of the discordant type.

Course in the Hospital—The patient's temperature rose occasionally to as high as 100 F. He offered no complaints except as to swelling of the legs and weakness, the latter condition improved after transfusions. He was ambulatory. He received intensive parenteral liver therapy, iron and copper, brewer's yeast and a diet high in calories. The peripheral edema was controlled with digitalis and mercurial diuretics. Transfusions of blood, some of which were followed by slight chills and elevation of temperature as high as 104 F, were necessary every three to four weeks. During the last weeks of the patient's life transfusions were given more often. Their effect, however, became short lived, edema and weakness increased, and after three months in the hospital the patient died, on Dec 29, 1943.

Necropsy—Autopsy was performed ninety-seven hours after death. The permission for autopsy did not include examination of the brain.

Gross Examination The body was well nourished. The skin was pale and slightly yellowish. The scleras were subicteric. The skin of the forearms and the dorsa of the hands was gray-brown. The jaws were edentulous, and the mucous membrane of the mouth was free from pigment. The tongue showed no atrophy. The thyroid gland was enlarged and well encapsulated and showed many yellowish cystic areas. The chest was barrel shaped, the lungs, emphysematous. Both ventricles of the heart were hypertrophied and dilated, the right proportionately more than the left. The myocardium was red-brown and showed slight fibrosis. The hepatic, mesenteric, renal, splenic and iliac vessels were free of thrombi, as was the portal vein.

The abdomen contained no free fluid. The liver was enormous, weighing 3,050 Gm, it reached to within 3 cm of the left axillary line at the level of the fifth rib. On the right it extended 8 cm below the costal

margin. Its color was a striking orange-brown. The capsule was thickened and irregularly opaque and contained numbers of petechial hemorrhages. The surface was finely nodular. On section the organ was extremely firm and gritty, and the color was uniform. Small irregular nodules outlined by gray-white streaks could be seen throughout the substance of the liver.

The gallbladder contained two soft concretions but was otherwise normal.

The pancreas was firm and of a lighter orange-brown tint than the liver. The lobular architecture was normal.

The spleen weighed 250 Gm. The capsule was slightly thickened. On section the organ was firm and dark red. The fibrous markings were increased.

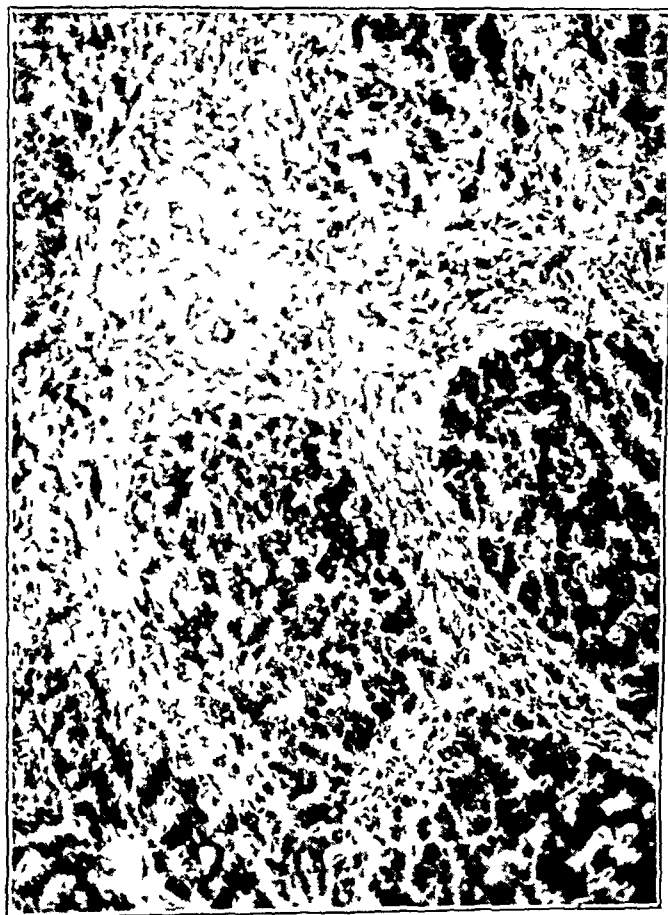


Fig 2—Periportal fibrosis dividing the liver into nodules. Even at this low magnification granules of dark pigment can be seen in the cytoplasm of some of the parenchymal cells. Masson's trichrome stain $\times 100$.

The esophagus did not contain varices. There was no abnormal pigmentation throughout the stomach and intestines.

The kidneys showed slight cortical scarring and were of normal size and color.

The adrenal glands appeared to be normal.

The hilar and mediastinal lymph nodes were anthracotic. The periaortic nodes were mottled rust and gray, while those of the peripancreatic and perihepatic regions were almost uniformly rust colored. They were all enlarged in varying degrees.

The ribs, the sternum and the vertebrae showed gray-red marrow. The cortex of these bones was not thickened.

There was edema of the lower part of the right leg but no abnormal pigmentation.

Microscopic Examination The following findings were noteworthy in the present connection. Small amounts of pigment were scattered through the alveoli of the lungs. Some of the pigment gave a positive reaction to stains for iron. Slightly larger amounts of perinuclear pigment in the heart muscle gave a similar reaction. In addition, there was the usual amount of unstained lipochrome. There was no demonstrable hemosiderin in the areas of fibrosis.

The liver was divided into irregular nodules by bands of fibrous tissue (fig 2). The parenchymal cells were



Fig 3—Acinar cells of the pancreas. Pigment granules appear black and in some cells are so densely clumped as to be indistinguishable from the nuclei. The connective tissue is increased. Iron stain, $\times 772$.

loaded with brown refractile pigment, much of which became blue with stains for iron. The most heavily laden cells were those about the portal areas. Many of the cells that were overcrowded with pigment seemed to be disintegrating. The Kupffer as well as the parenchymal cells were similarly affected. The periportal fibrous tissue was increased and contained large clumps of intracellular and extracellular hemosiderin and unstained brown pigment. The epithelial cells of the bile ducts were likewise pigmented. There was moderate proliferation of small bile ducts but little apparent regeneration of parenchymal cells. In addition to these changes there were thickening of the central vein and disintegration of the cells of the liver in the vicinity. There were moderate numbers of areas of extramedullary hemopoiesis.

The pancreas showed large amounts of hemosiderin in the acinar cells (fig 3) as well as in the epithelium of the ducts. There was increase in fibrous tissue, and in it were clumps of iron-containing pigment. The islets were large and were frequently surrounded by fibrous tissue. A moderate amount of iron pigment was present in the islet cells. The parenchyma and the islets had undergone rather severe autolysis (fig 4). However, it seemed that most of the pig-

mented cells in the islets were still fairly well preserved, while those of the acinar tissue were necrotic. Phagocytes with granules of pigment were also demonstrable.

Sections of the spleen showed chronic passive congestion with a few small islands of extramedullary hemopoiesis. Stains for iron confirmed the observation made in sections stained with hematoxylin and eosin that there was a small amount of diffusely scattered iron-containing pigment.

The cortex of the adrenal glands and the epithelial cells of the thyroid and prostate glands also contained hemosiderin.

Unfortunately, no sections of the testis, the gastrointestinal tract or the skin were available.

The lymph nodes were large. They contained hemosiderin. The perihepatic and peripancreatic nodes were most heavily burdened, while the mediastinal nodes contained only small amounts. Again there was little extramedullary hemopoiesis.

In sections from the ribs, the sternum and the vertebrae stained with hematoxylin and eosin and with Giemsa's stain the marrow cells were mainly of the erythropoietic type. Their number was increased at the expense of fat. Their number was about equally divided between stem cells and pronormoblasts, with fewer normoblasts. There was also a moderate number of mature red cells. There was depression of the white blood cell series. Only an occasional mature polymorphonuclear cell was visible. Megakaryocytes were

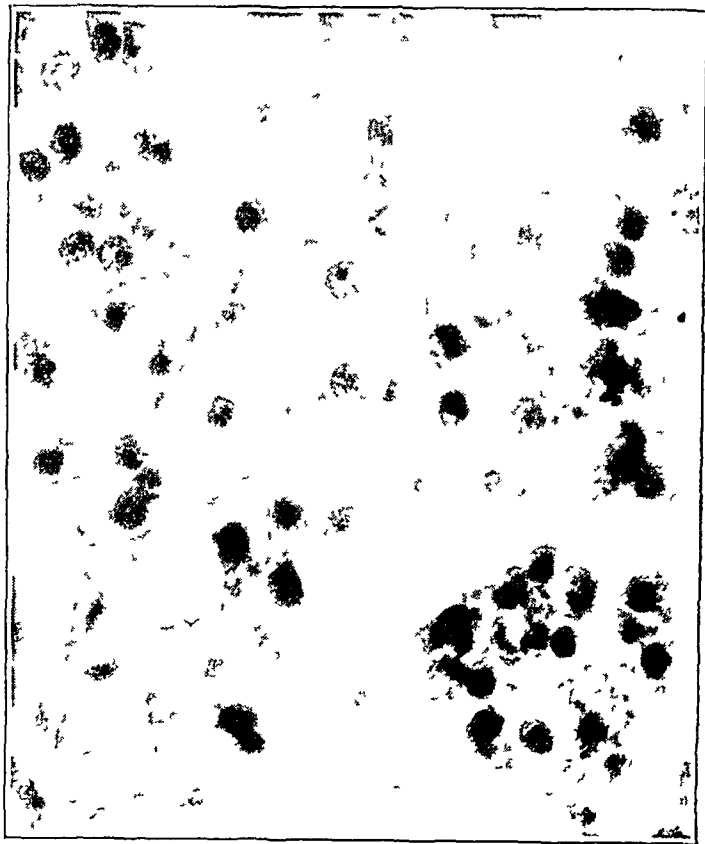


Fig 4—Islet cells of the pancreas. Pigment visible as dark granules in the cytoplasm of the cells. Iron stain, $\times 772$.

seen in decreased numbers. The cortex and the periosteum were not unusual.

The bone marrow as seen at autopsy showed, when compared with that in the smear from the sternum taken in October 1943, regression toward a more immature state. The stem cells were extremely pale, large, basophilic and poor in chromatin. The pronormoblasts were smaller, with clearly differentiated nuclei and one or more nucleoli. The more mature normo-

blasts were about the size of lymphocytes, with dense "clock face" nuclei and rims of basophilic cytoplasm.

The kidneys showed mild cortical scarring. Pigmentation was present but was confined almost exclusively to the epithelium of the ascending loops of Henle and to the cells of the distal convoluted tubules.

The amount of fibrous tissue in the liver of this patient with anemia, while not as great as that in the liver of the average person with idiopathic hemochromatosis, was extensive enough to warrant the diagnosis of portal cirrhosis. The amount of fibrous tissue and pigment that was demonstrated in the pancreas was even greater than that in the average patient with hemochromatosis, while the spleen showed less iron pigment.

Stains of the bone marrow for iron showed less hemosiderin than is seen in the average patient with hemochromatosis.

Anatomic diagnoses included pseudoaplastic anemia of unknown origin, extramedullary hemopoiesis (mild) hemochromatosis, portal cirrhosis, hepatosplenomegaly, coronary sclerosis, cardiac hypertrophy and dilatation, myocardial fibrosis, pulmonary emphysema and fibrosis, pyelitis cystica, edema of the right lower extremity and nodular hyperplasia of the thyroid gland.

COMMENT

The significance of the coexistence of hemochromatosis and aplastic anemia in the 6 patients who had had repeated transfusions is obscure.

The distinction between hemochromatosis and advanced hemosiderosis rests on rather insecure foundations. Muir and Shaw Dunn¹⁹ emphasized pigmentation of the heart muscle, the adrenal cortex, the thyroid gland, the ependyma of the ventricle and the smooth muscle of the intestines in hemochromatosis, stating that it does not occur as a result of hemolysis. The same and other investigators²⁰ have noted the absence of cirrhosis of the liver in persons with marked hemosiderosis due to pernicious anemia, despite the fact that numerous transfusions were given. Still others²¹ have pointed out the difference of distribution in the kidney, stating that in hemosiderosis the proximal convoluted tubules are affected, whereas in hemochromatosis the ascending loops of Henle and the distal convoluted tubules are involved.

19 Muir, R, and Shaw Dunn, J. Iron Content of Organs in Bronzed Diabetes, *J Path & Bact* **19** 226, 1914.

20 (a) Wintrobe, M. M. *Clinical Hematology*, Philadelphia, Lea & Febiger, 1943. (b) Whitby and Britton.¹ (c) Yates, J. L., and Thalhimer, W. Treatment of Pernicious Anemia (A Patient Who Received 113 Transfusions), *J A M A* **87** 2156 (Dec 25) 1926. (d) Jones, H. W. Prolonged Blood Transfusions in Pernicious Anemia, *ibid* **86** 1673 (May 29) 1926.

21 Gaskell, J. F., Mackenzie Wallis, R. L., Sladden, A. F., Vaile, P. T., and Garrod, A. E. Contribution to the Study of Bronzed Diabetes, *Quart J Med* **7** 129 (Jan) 1914.

Rous and Oliver²² attempted to produce hemochromatosis by giving transfusions of 10 to 15 cc of blood to rabbits daily for periods up to six and one-half months. In addition to large amounts of hemosiderin in the liver, they found deposits in the adrenal cortex, the submaxillary glands, the cartilages of the trachea, and the skin and large deposits in the kidneys. The pancreas was affected only in animals subjected to this procedure for a considerable length of time and then only slightly. Furthermore, the kidneys held heavy deposits in contrast to the sparse pigmentation in hemochromatosis. No pigment was found in the thyroid gland. These workers noted cirrhosis of the liver in 2 of the 3 rabbits but felt that it was an unrelated finding.

Hueck²³ emphasized the sparse distribution of hemosiderin in the spleen, the bone marrow and the kidneys in hemochromatosis in contrast to the abundant pigmentation of these organs in hemosiderosis. He expressed the opinion that the presence or the absence of hemofuscin is an important point for purposes of differentiation. However, there are two theoretic objections to this concept.

1. Much of the "non-free" pigment in hemochromatosis is found to contain iron when subjected to careful technic, and therefore the amount of hemofuscin varies.

2. In the present state of knowledge of the composition of hemofuscin, we see no reason why it should not exist in hemosiderosis.

There are many writers, principally of the French school²⁴ who do not make any distinction between hemochromatosis and hemosiderosis. An excellent discussion of the subject is presented by Sheldon,¹² who concluded that there are differences in distribution in the spleen, the bone marrow and the kidneys but maintained that a certain similarity exists, since the body tends to distribute hemosiderin by a common mechanism, whatever the source of the iron.

Whipple and Bradford,²⁵ in reporting 8 cases of Cooley's anemia, noted the distribution and

22 Rous, P., and Oliver, J. Experimental Hemochromatosis, *J Exper Med* **28** 629 (Nov) 1918.

23 Hueck, W. Haemochromatose, in Krehl, L., and Marchand, F. *Handbuch der allgemeinen Pathologie*, Leipzig, S. Hirzel, 1921, vol 3, pt 2, p 371.

24 Roque, G., Chalié, J., and Nove-Josserand, L. Étude critique sur la conception des cirrhoses pigmentaires. Origine hemolytique de leur siderose, *Rev de med, Paris* **33** 353 (May) 1913.

25 Whipple, G. H., and Bradford, W. L. Racial or Familial Anemia of Children Associated with Fundamental Disturbances of Bone and Pigment Metabolism (Cooley-von Jaksch), *Am J Dis Child* **44** 336 (Aug) 1932, Mediterranean Disease-Thalassemia (Erythroblastic Anemia of Cooley), *J Pediat* **7** 279 (Sept) 1936.

types of pigment and concluded that they were similar to those of hemochromatosis. However, these writers did not find an accompanying cirrhosis of the liver.

From experimental and pathologic evidence, the anatomic basis for a diagnosis of hemochromatosis as opposed to hemosiderosis rests on the following criteria:

1. The presence in hemochromatosis of portal cirrhosis in addition to large amounts of hemosiderin in the liver.

should be a high incidence of hemochromatosis in the hemolytic and pernicious anemias. That this is not true is shown by numerous reports in the literature²⁶ on these diseases. Secondly, one should be able to reproduce hemochromatosis experimentally by repeated transfusions,²² by hemolytic agents²⁷ and by injections of hemoglobin²⁸ and of dialyzed iron.²⁹ Such attempts have been unsuccessful. Finally, that the availability of iron stored in the liver for synthesis of hemoglobin differs in hemochromatosis and in

Principal Features of Reported Cases of Aplastic Anemia Associated with Hemochromatosis

Author	Age at Onset, Sex	Duration, Yr	Age at Death, Yr	Blood Counts on Admission	Amount of Transfused Blood	Diabetes	Bone Marrow	Summary of Autopsy
Kark, R. M.	30 ♂	10	40	RBC 2,500,000 Hb 50% CI 1 WBC 3,500	290 transfusions in 9 years	Hyperglycemia, no glycosuria	No aplasia, cellular	No autopsy, pigmentation of skin (biopsy) conjunctivas and teeth, enlargement of liver
Mackey, R.	46 ♂	3½	49½	RBC 1,050,000 Hb 22% CI 108 WBC 4,100	39.8 liters	Not mentioned	Selective aplasia of erythropoiesis	Pigmentation of lymph nodes, pancreas and heart muscle, fibrosis and pigmentation of liver
Bomford, R. R. and Rhoads, C. P.	51 ♂	2½	53½	RBC 1,400,000 Hb 30% CI 107 MCV 90 cu μ Retic 1.4% WBC 1,150 Platelets 68,000	16 transfusions	Not present	Cellular	Pigmentation of skin and lymph nodes, fibrosis and pigmentation of liver and pancreas
	68 ♂	2	70	RBC 1,300,000 Hb 35% CI 13 MCV 104 cu μ Retic 1.4% WBC 4,350	12 transfusions	Not present	Cellular	Pigmentation of skin, lymph nodes, adrenal glands and choroid plexus, fibrosis and pigmentation of liver and pancreas
	12 ♂	9	21	RBC 1,300,000 Hb 26% CI 1 MCV 86 cu μ Retic 0.4% WBC 3,850 Platelets 60,000	54 transfusions	Glycosuria	Cellular	Pigmentation of skin, lymph nodes, adrenal glands and cardiac muscle, fibrosis and pigmentation of liver and pancreas
Authors' case	64 ♂	1	65	RBC 1,500,000 Hb 35% CI 12 MCV 100 cu μ Retic 3.1% WBC 4,900 Platelets 216,000	12.8 liters, 17 transfusions	Hyperglycemia, no glycosuria	Cellular	Pigmentation of skin, lymph nodes, adrenal glands, kidneys, heart muscle, lungs and thyroid and prostate glands, fibrosis and pigmentation of liver and pancreas

2. Increased fibrous tissue in the pancreas with deposits of pigment in the islet cells as well as in acinar cells and the epithelium of the ducts.

3. The relatively small amount of pigment in the kidneys, the spleen and the bone marrow.

The case reported here fulfilled all these requirements and, in addition, presented, clinically, an elevated curve of tolerance for dextrose, signifying pancreatic damage.

We believe that intense hemosiderosis is an entity. If hemochromatosis and hemosiderosis were different degrees of the same process, there

hemosiderosis is seen from the experiments of Muir and Shaw Dunn³⁰ and of Whipple and his

²⁶ Whitby and Britton¹ Wintrobe^{20a}

²⁷ Muir, R., and Shaw Dunn, J. Retention of Iron in Organs in Haemolytic Anaemia, *J. Path. & Bact.* **19** 417, 1914.

²⁸ Muir, R., and Young, J. S. Relation of the Liver to the Disposal of Haemoglobin, *J. Path. & Bact.* **35** 113 (Jan.) 1932.

²⁹ Polson, C. J. The Fate of Colloidal Iron Administered Intravenously. Long Experiments, *J. Path. & Bact.* **32** 247 (April) 1929.

³⁰ Muir, R., and Shaw Dunn, J. Absorption of Iron from the Organs After Haemolysis, *ibid.* **20** 41, 1915.

co-workers³¹ It is therefore unlikely that transfusions in a patient with pseudoaplastic anemia could be responsible for hemochromatosis

In the accompanying table the essential features of the reported cases of aplastic anemia associated with hemochromatosis are given With the exception of the patient in the third case, who lived above a garage and complained of the odor of fumes, no patient gave a history of exposure to potentially toxic substances Both Kark⁸ and Mackey⁹ attributed the development of hemochromatosis in their patients to the inability of the body to utilize or excrete the iron introduced in the form of hemoglobin The latter writer felt that the amount of iron recovered from the patient's liver was directly related to the amount of hemoglobin administered in transfusions Bomford and Rhoads⁵ did not commit themselves regarding the relationship of hemochromatosis to transfusions and stated that 2 of their patients had not received an exceptional number of transfusions

In our case the liver contained the excessive amount of 29 Gm of iron During the entire illness our patient received 12.8 liters of blood in seventeen transfusions Only about 6.5 Gm of iron was introduced into the body by this means This leaves an excess of 22.5 Gm of iron

Studies of the excretion of urobilinogen by patients with pseudoaplastic anemia indicate increased hemolysis in many instances⁵ This factor may account for some of the iron present in the organs of our patient

Although no studies of the metabolism of porphyrin were done in our case, there is evidence that the pigment metabolism in aplastic anemia differs from that in any other type of anemia The increased excretion of type III coproporphyrin which occurs in some instances of aplastic anemia³² is also found in lead poisoning³³ and after the administration of arsphen-

amine³⁴ and sulfanilamide³⁵ On this basis, Dobriner, Rhoads and Hummel³⁶ suggested that aplastic anemia may result from intoxication It is interesting to note that Kark's patient,⁸ reported as having the first case of aplastic anemia and hemochromatosis, had, in addition to pigmentation of the skin and of the conjunctivas, discoloration of the teeth one of the classic symptoms of congenital porphyria So far as we know, discoloration of the teeth associated with hemochromatosis has never been described Disturbances of the metabolism of porphyrin occur frequently in diseases of the liver³⁶ and have been noted in patients with hemochromatosis³⁷ This fact raises the question whether the porphyrinuria occurring in various intoxications in aplastic anemia, in hemochromatosis and in diseases of the liver is not due entirely to hepatic dysfunction

In our case sulfobromophthalein excretion and cephalin flocculation tests gave negative results Only the abnormal response to parenterally administered synthetic vitamin K suggested damage to the liver³⁸ Barker,³⁹ using various tests of hepatic function, found evidence of damage to the liver in more than half of his patients with all types of anemia

That hemochromatosis is due to an inborn error of intracellular iron metabolism is generally recognized⁴⁰ However, some investigators⁴¹ have emphasized the importance of the cirrhosis

34 Hoerbinger, W, and Fink, H Ueber Porphyrine bei klinischer Porphyrie, *Ztschr f physiol Chem* **236** 136, 1935

35 Rimington, C, and Hemmings, A W Porphyrinuria Following Sulphanilamide Sulphanilamide Dermatitis, *Lancet* **1** 770 (April 2) 1938

36 (a) Nesbitt, S Excretion of Coproporphyrin in Hepatic Disease IV Isolation and Identification of Urinary Coproporphyrin Isomers, *Arch Int Med* **71** 483 (April) 1943 (b) Dobriner, K Urinary Porphyrins in Disease, *J Biol Chem* **113** 1 (Feb) 1936

37 Dobriner^{36b} Dobriner, K Porphyrin Excretion in the Feces in Normal and Pathological Conditions, *J Biol Chem* **120** 115 (Aug) 1937 Vannotti, A Porphyrine und Porphyrinkrankheiten, Berlin Julius Springer, 1937, p 145 Lageder, K Klinische Porphyrinuntersuchungen mit einer quantitativen spektroskopischen Methode, *Arch f Verdauungskr* **56** 237 (Nov) 1934 Eppinger, H Die Leberkrankheiten, Berlin, Julius Springer, 1937, p 426

38 Data concerning the test referred to will be presented in another communication, by Dr Shepard Shapiro

39 Barker, W H Excretion of Bile Pigment and Hepatic Function in Diseases of the Blood, *Arch Int Med* **62** 222 (Aug) 1938

40 Dry, T J Hemochromatosis Its Relation to the Metabolism of Iron and Copper, *Minnesota Med* **17** 301 (June) 1934 Sheldon¹² Butt and Wilder¹⁴

41 Potter, N B, and Milne, L S Bronzed Diabetes, *Am J M Sc* **143** 46 (Jan) 1912 Gaskell and others²¹

31 Whipple, G H, and Rabschitt-Robbins, F S Hemoglobin Production Factors in the Human Liver, *J Exper Med* **57** 671 (April) 1933, Hemoglobin Production Factors in the Human Liver, *ibid* **76** 283 (Sept) 1942 Balfour, W M, Hahn, P F, Bale, W F, Pommerenke, W T, and Whipple, G H Radioactive Iron Absorption in Clinical Conditions Normal, Pregnancy, Anemia, and Hemochromatosis, *ibid* **76** 15 (July) 1942

32 Dobriner, K, Rhoads, C P, and Hummel, L E Excretion of Porphyrin in Refractory and Aplastic Anemia, *J Clin Investigation* **17** 125 (March) 1938

33 Watson, C J Concerning the Naturally Occurring Porphyrins Urinary Porphyrin in Lead Poisoning as Contrasted with That Excreted Normally and in Other Diseases *J Clin Investigation* **15** 327 (May) 1936

of the liver. In contrast to idiopathic hemochromatosis, there is evidence that increased hemolysis is a factor in the evolution of hemochromatosis associated with pseudoaplastic anemia. Additional factors, however, must be operative to produce the lesions of hemochromatosis as distinct from those of hemosiderosis.

The cause of aplastic anemia is obscure, but its relationship to exogenous and endogenous toxins⁵ is assumed. Such toxic elements, possibly in connection with deficiency factors, may lead to permanent damage to the liver. Thus, patients with pseudoaplastic anemia with prolonged course come to have retention of iron pigmentation, and cirrhosis of the liver and, as the pancreas becomes involved, diabetes develops.

SUMMARY AND CONCLUSIONS

Although both aplastic anemia and hemochromatosis are comparatively rare diseases, their occurrence together has been recorded in 5 instances, an incidence which, we believe, is altogether too high to be regarded as accidental. In 4 of the 5 cases referred to the changes in the bone marrow were described as pseudoaplastic.

The case which we have reported here is that of a patient with pseudoaplastic anemia whose body at autopsy revealed the lesions that are characteristic of hemochromatosis. Similarities occur be-

tween hemosiderosis, which is frequently found in certain anemias, and hemochromatosis, in which anemia, if present, is merely a complicating factor. Hemosiderosis and hemochromatosis are, we believe, separate disease entities.

In an attempt to correlate the changes in pseudoaplastic anemia with those in hemochromatosis we have considered the question of the origin of the iron in both conditions together with the available evidence of hepatic dysfunction.

The iron derived from the destruction of intrinsic and of transfused blood is not used in the formation of hemoglobin but is mechanically deposited in various organs. If the aplastic anemia is of sufficient duration, large quantities of iron accumulate. We believe that view to be sound which holds that aplastic anemia is due to toxins. These toxins, together with other factors, possibly nutritional, may lead to permanent hepatic damage in the form of cirrhosis. The increased amount of iron in the presence of cirrhosis of the liver produces a picture indistinguishable from that of hemochromatosis.

In contrast to idiopathic hemochromatosis, increased hemolysis is active in the production of hemochromatosis when it is associated with pseudoaplastic anemia.

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PERNICIOUS ANEMIA IN CHINESE

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Pernicious anemia has generally been considered a disease of Caucasians. In a recent review¹ we pointed out that its occurrence in Negroes is by no means uncommon and that the recognition of this fact should make for more frequent diagnosis. Textbooks in general, and hematologic texts in particular, stress the great infrequency of pernicious anemia in Chinese. This impression is borne out by a study of the literature. Notwithstanding this fact, we have had occasion to recognize and study 3 cases of typical pernicious anemia in native-born Chinese who had lived for many years in the Chinese community of Chicago.

REVIEW OF THE LITERATURE

The cases reviewed by Struther² were incompletely worked up and did not fulfil the diagnostic criteria of pernicious anemia. In response to his questionnaire, Berglund wrote that no Chinese patient with this disease had been seen at the Peking Hospital. Fu and Sturton³ reported a case in Hangchow, but the records concerning the gastric juice and the nervous system were incomplete. Morris⁴ found 6 cases in the hospital records of Central and North China, but these were not documented, and in his own experience there were no proved cases. Williams'⁵ report of a case was also incomplete, and his patient improved after four weeks in the hospital without liver therapy. The patient's further course was not followed.

De Langen and Lichtenstein⁶ stated that they had never seen pernicious anemia among the

poor Chinese in Batavia but that an occasional case has been observed among the wealthier patients.

According to Snapper⁷, macrocytic nutritional anemia occurs frequently in the Orient, but true pernicious anemia is rare. The 6 cases reported by him from the Peiping Union Medical College Hospital had features which were atypical for pernicious anemia. The patients responded to small doses of liver and remained free from recurrences for years without liver therapy or with only small doses of liver. They showed rapid improvement of extensive neurologic changes with liver therapy or sometimes with adequate diet alone. There was a return of free hydrochloric acid with the disappearance of the anemia, and the expected anisocytosis and poikilocytosis were absent from the blood. Snapper expressed the opinion that "it seems hardly feasible to conclude that this group of patients really suffered from genuine pernicious anemia, although one may still readily agree that their anemia was closely related to pernicious anemia."

Yang and Keefer⁸ have reported the only 2 cases of pernicious anemia in Chinese observed previously on this continent. They were cases of Minot's and apparently were typical.

REPORT OF CASES

CASE 1—H T Y, a 55 year old man, a native Chinese, was admitted to the hospital Jan 29, 1935, because of vomiting of one week's duration, loss of weight, anorexia and weakness of six months' duration and tingling of the fingers and toes and soreness of the tongue of one year's duration. Physical examination revealed nothing abnormal except extreme pallor and atrophy of the papillae of the tongue. Examinations of the sputum, stools, urine and spinal fluid were non-contributory. Roentgen ray examination of the gastrointestinal tract revealed nothing abnormal. No free acid and 10 degrees of total acid were found in tests of the contents of the stomach after an Ewald meal. Hematologic values were typical of pernicious anemia in relapse (chart 1). Response to liver therapy was satisfactory, and he was discharged from the hospital on March 16. He received liver therapy as an outpatient until June 20, when he disappeared from observation until Nov 14, 1936. At that time he again presented himself in a state of relapse. Response to therapy was satisfactory, and

7 Snapper, I. Chinese Lessons to Western Medicine, New York, Interscience Publishers, Inc., 1941, p 264.

8 Yang, C S, and Keefer, C S. Pernicious Anemia in Chinese Patients, Nat M J China 17 218, 1931.

Aided by a grant from the Wilson Laboratories

From the Hematology Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital

1 Schwartz, S O, and Gore, M. Pernicious Anemia in Negroes, Arch Int Med 72 782 (Dec) 1943

2 Struther, G. Discussions of Anemias in China, Chinese M J 43 818, 1929

3 Fu, W T, and Sturton, S D. A Severe Case of Pernicious Anemia, Chinese M J 40 1016, 1926

4 Morris, H H. Anemia in China, Chinese M J 43 768, 1929

5 Williams, T H. Pernicious Anemia in Szechwan, Chinese M J 46 673, 1932

6 De Langen, C D, and Lichtenstein, A. Text-book of Tropical Medicine, Batavia Java, G Kolff & Co, 1936, p 487

he continued well until January 1940 with somewhat intermittent treatment. He was last seen on Sept 3, 1941. He was in good health and had had no liver except small amounts eaten occasionally. The achylia was still in evidence on the second admission.

CASE 2—W L Y, a 60 year old man, a native Chinese, was admitted to the hospital June 6, 1940, complaining of soreness of the tongue, difficulty in swallowing, loss of weight, numbness of the fingers and

of writing. The achlorhydria—even after injections of histamine—was still present on July 28, 1944.

CASE 3—L B, a 73 year old man, a native Chinese, was first admitted to the hospital on March 1, 1943. Because of his inability to speak English and his extreme illness, no history was elicitable. The extreme pallor, vitiligo of the skin and jaundice of the scleras were the most prominent observations made in the examination. There was noted, in addition, a greatly

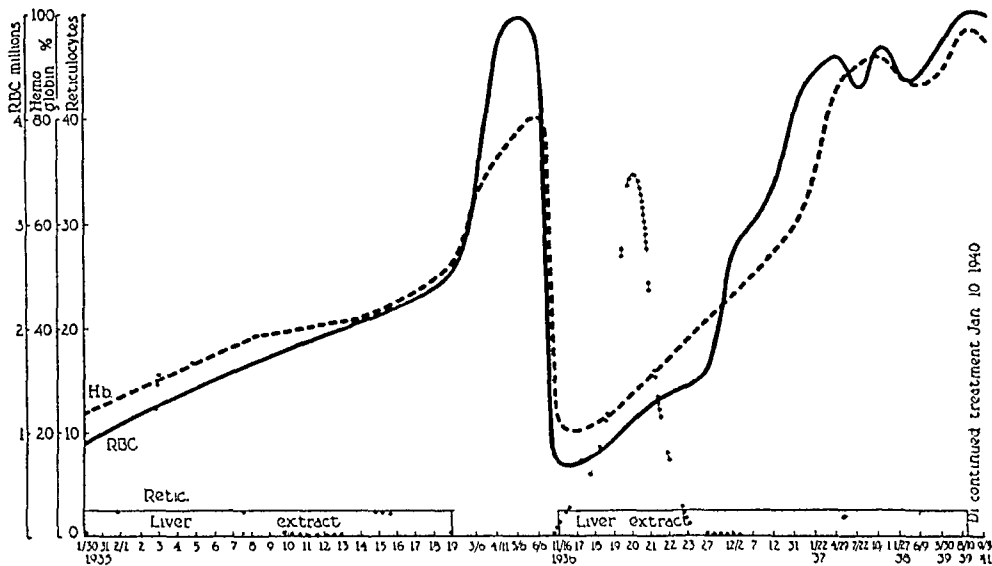


Chart 1 (case 1) —Characteristic reticulocyte response and rise in red cells and hemoglobin following administration of liver, with relapse after the discontinuance of therapy and a second response almost identical with the first

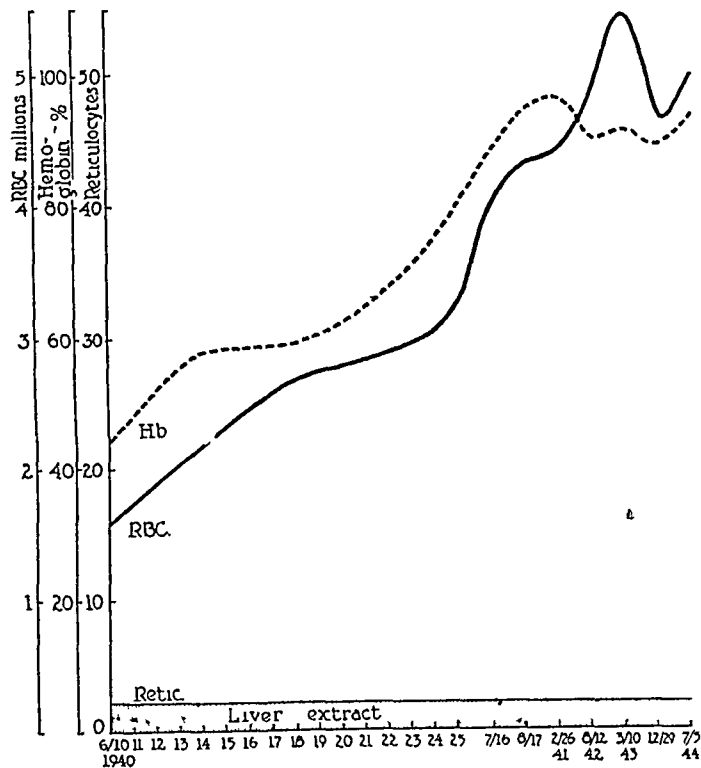


Chart 2 (case 2) —Typical red cell, hemoglobin and reticulocyte response following liver therapy

vertigo. On examination he was found to have a smooth, red tongue, jaundice of the scleras and hyperactive knee jerks. Laboratory findings of interest were a histamine-fast achlorhydria and an icterus index of 15. Hematologic values were typical of pernicious anemia in relapse (chart 2). Response to liver therapy was satisfactory, and the patient has been maintained in good health with average amounts of liver extract to the time

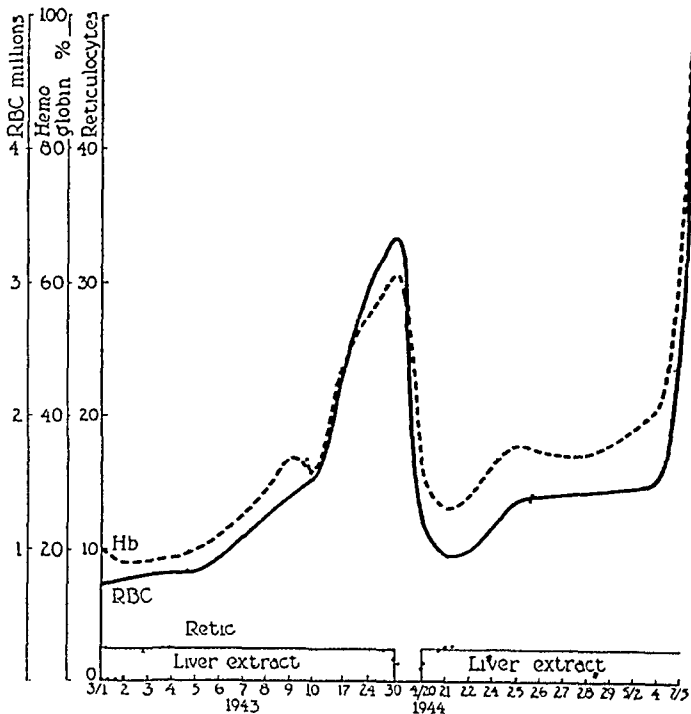


Chart 3 (case 3) —Response resembling that in case 1. It is to be noted that therapy was discontinued before complete remission occurred after the first course of treatment, and yet more than a year elapsed before the second relapse

distended bladder which extended to within a few centimeters of the umbilicus. Laboratory findings of interest were the decidedly elevated icteric index (37), the histamine-fast achlorhydria and the hypercellular marrow with typical megaloblastic maturation of the cells. Hematologic values were typical of pernicious anemia in relapse (chart 3) and improved rapidly with liver therapy alone. On March 30 he left the hospital, but,

failing to return for injections of liver extract, he re-entered in relapse on April 20, 1944. The findings at this time were essentially as previously noted, except that the icteric index now was only 21. He again responded uneventfully and was discharged on May 4. Since then he has been cared for in the outpatient clinic and has been well maintained. The jaundice has disappeared. Symptoms referable to the bladder are absent. The achlorhydria has persisted (rechecked with histamine July 28, 1944).

COMMENT

Using for criteria of pernicious anemia the macrocytic anemia (with the accompanying anisocytosis and poikilocytosis), the permanent achlorhydria, megaloblastic cell maturation, signs of increased pigmentary metabolism, neurologic changes and remission after the exhibition of liver therapy and relapse following its withdrawal,⁹ one notes that all 3 cases are typical instances of Addison's (pernicious) anemia of the type seen in the Caucasian. These criteria are outlined in the table.

Characteristic Clinical and Laboratory Observations in the Three Reported Cases

	Case 1	Case 2	Case 3
Macrocytic anemia	+	+	+
Permanent achlorhydria	+	+	+
	(Only once examined)		
Megaloblastic cell maturation	No studies of the marrow	No studies of the marrow	+
Evidences of increased pigmentary metabolism	No pigmentary studies	+	+
Neurologic changes	+	+	+
Remission after liver therapy	+	+	+
Relapse after discontinuance of liver therapy	-	Has not discontinued therapy	+

The fact that we could encounter, in a relatively short period of time and in an institution

9 Schwartz, S. O., and Legere, H. Relapses in Pernicious Anemia, J. A. M. A. 124: 637 (March 4) 1944.

in which orientals are relatively rare, 3 Chinese with this disease which is said to occur with extreme rarity in members of this race in their native environs raises some interesting questions. Is pernicious anemia really rare in the Chinese of China, or is it their relatively infrequent contact with western physicians which merely makes it appear so? Has the teaching that pernicious anemia is rare in the Chinese influenced some clinicians to prefer to interpret the macrocytic anemia as one secondary to malnutrition rather than to accept it as true pernicious anemia? We are in no position to answer these questions. Or does pernicious anemia appear only when the native is transplanted to a new (and apparently unfavorable) environment? If this is the case, then one may ask whether it is the physical environment or the changed dietary habits that induce the anemia.

There is certainly no evidence that physical environment plays a significant role. Dietary habits could be a factor, but such a conclusion would seem to be a paradox in view of the generally accepted belief that the American diet is nutritionally superior. Two other possibilities suggest themselves. The first is that environmental, infective, nutritional and perhaps physical circumstances leading to gastritis may in time sufficiently interfere with production of the intrinsic factor to give rise to pernicious anemia. The second possibility is that the increased fat in the American diet may be a cause.¹⁰

With the increasing interest in China and the probability of more opportunity to study the Chinese, it will be of considerable interest to see whether more cases of pernicious anemia in Chinese will come to light.

10 Johnson, V., Freeman, L. W., and Longm, J. Erythrocyte Damage by Lipemic Serum in Normal Man and in Pernicious Anemia, J. A. M. A. 124: 1250 (April 29) 1944.

LARGE DOSES OF ASCORBIC ACID IN TREATMENT OF VITAMIN C DEFICIENCIES

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AND

DOROTHY HAGEDORN, BS

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Patients entering a hospital with a variety of complaints are often found to have low levels of ascorbic acid in the plasma if determinations of this factor are made. In some cases in which diagnosis or treatment may be facilitated by the restoration of vitamin C in the tissues, rapid saturation is desired. To accomplish this efficiently, it is necessary to determine the maximum dose that will not cause increased urinary excretion of ascorbic acid. Obviously the total dose required for saturation depends on the state of deficiency of the body tissues, and one can judge that amount only by some indirect index of the status of the tissues. It has been argued that the plasma level of ascorbic acid is a poor index and attempts have been made to find more reliable criteria for the state of vitamin C nutrition. Studies of excretion, although extensive, have not established a definite normal standard. Experiments concerning saturation have furnished valuable data but still have not proved whether good vitamin C nutrition entails a saturation level or something less. The level of ascorbic acid in the whole blood has been suggested¹ as being more truly representative of the general body status of vitamin C nutrition than the level in the plasma, since the cell content of this vitamin does not fluctuate as rapidly as does the plasma content. Further reasoning along this line has led some investigators^{1b} to prefer the use of the white cell and platelet layer of the blood as an index of vitamin deficiency in the tissues. It was noted that the white blood cells retained appreciable amounts of vitamin C after the plasma content was reduced to very low levels, and therefore it was argued that plasma values did not reflect tissue need. However, it must be remembered that vitamin C is

not evenly distributed throughout the body tissues. In the ovaries and in the adrenal and the pituitary glands, for example the concentration is much higher than in some of the other glands or in muscle. Until the mechanism of function is known, the separate needs of the different tissues for this vitamin cannot be evaluated. The plasma obviously is the vehicle of transport and might not reflect deficiency in the tissues if extensive storage of vitamin C occurs. There is little evidence that much is stored, in which case persistently low plasma levels of vitamin C must mean deprivation somewhere along the route. In any event, when a vitamin C deficiency is suggested clinically and the dietary history is poor, a low plasma value is corroborative evidence. Our observations in connection with this and other studies have led to the belief that persons, sick or well, who regularly include adequate amounts of vitamin C-containing food in the diet and who have no evidence of oral disease seldom have fasting plasma values lower than 0.8 mg per hundred cubic centimeters. The amount of administered ascorbic acid retained by the body may indicate the state of depletion in the tissues, but in excretion tests collection of specimens is more time consuming and not always convenient, besides which the assay itself (as in the case of determinations of whole blood or of white cell content) is not as simple as determination of plasma content of vitamin C. Therefore in addition to observations on the efficiency of large doses of ascorbic acid in treatment of vitamin C deficiency we have presented some data on plasma levels at the various stages of depletion up to saturation with corresponding excretions of the various doses of ascorbic acid in an attempt to further the knowledge that would justify the clinical use of this convenient test.

MATERIALS AND METHODS

The data here reported for 26 hospital patients, unselected as to disease except for clinical and laboratory indications of vitamin C deficiency, include determina-

From the Department of Medicine of the University of Wisconsin

1 (a) Heinemann, M. The Distribution of Ascorbic Acid Between Cells and Serum in Relation to Its Urinary Excretion, *J Clin Investigation* **17** 751 (Nov) 1938. (b) Butler, A. M., and Cushman, M. Distribution of Ascorbic Acid in the Blood and Its Significance, *ibid* **19** 459 (May) 1940.

tions of levels in plasma, whole blood and urine, before and after large oral doses of ascorbic acid or intravenous injections of sodium ascorbate

The method used for determinations of vitamin C in whole blood and urine was that of Roe and Kuether², for determinations in plasma, the Mindlin-Butler macro-method³. Determinations of levels in whole blood and in plasma were made within a three hour period after the blood samples were obtained. Determinations of urinary levels were made on fresh material for most of the fractional specimens, and twenty-four hour specimens were examined as soon as the collection period was ended. All urine was kept in brown bottles placed in a container with ice, and when the collection period was prolonged, glacial acetic acid was added as a preservative. Duplicate readings on fresh and on preserved aliquots of the same specimen showed no loss of ascorbic acid by this method of preservation over a twenty-four hour period.

The clinical selection of patients for this study was based on dietary history suggesting gross deficiency of raw fruit and vegetable foods or on visible evidence of edema, redness, retraction or inflammation of the gums or of frank pyorrhea alveolaris.

TABLE 1—Efficiency of Large Doses of Ascorbic Acid

Number of Doses		Dose, Mg	Excretion of Ascorbic Acid		
Intra venous	Oral		Mg /Hour		Average, Mg /24 Hours
			Average	Range	
6	9	100	0.33	0.2-0.5	7.9
6	5	200	0.32	0.04-2.3	13.6
	10	300	0.34	0.04-0.7	8.3
	19	400	0.35	0.06-1.2	8.3
4	10	500	0.33	0.2-3.0	19.9
	3	1 Gm	0.50	0.3-0.6	12.0
Basic excretion of 11 subjects			0.24	0.03-0.44	5.7

RESULTS AND COMMENT

In table 1 a condensation of part of the data shows that single doses as high as 1 Gm of ascorbic acid were given without significant urinary loss. A variation in the number of hours of collection of urine with different doses is the result of an attempt at detail by fractionating all specimens of urine when the daily dose was divided, so that each specimen included the immediate excretion after one dose of ascorbic acid. Therefore, as shown in table 1, the average excretion for a twenty-four hour period was in many instances obtained from figures on twenty-four hour excretion calculated on the

basis of actual excretion each hour for fractional periods varying from three to fifteen hours. In 11 subjects the twenty-four hour excretion of ascorbic acid prior to supplementation with doses of the vitamin ranged from 2 to 11 mg. Because plasma levels for the group were within the same range, we did not delay treatment in every case to determine pretreatment excretion. The plasma level (and occasionally the whole blood level) was determined in all but 1 instance. These basic levels were between 0 and 0.39 mg per hundred cubic centimeters, except for subject 1 in table 2.

Averages for 200 and 500 mg doses are out of line because of the inclusion of figures on intravenous doses. This method of administration tended to produce higher excretions, as already indicated by van Eekelen and Heinemann⁴. Inspection of table 2 shows that in every instance intravenous therapy resulted in a larger excretion than did an oral dose of the same amount in the same or in different patients, when plasma levels were similar, as, for example in subjects 22 and 23. However, the magnitude of this difference in excretion between oral and intravenous administration is not such as to constitute a large fractional loss of the dose administered while the patient is still seriously deficient in vitamin C.

Daily doses of ascorbic acid and the results of administration of various amounts are presented in table 2. The table gives a more accurate picture of the correlation between plasma and excretion and of the efficiency of rapid saturation. All plasma readings were made on fasting blood samples, that is, from blood drawn in the morning before breakfast, at least twelve hours after ingestion of food or ascorbic acid. During the period in which ascorbic acid was administered, the pairing of values for excretion and for plasma was based on the blood sample which was obtained at the end of the twenty-four hour period of collection of urine. Complete data on all patients could not be obtained for several reasons. However, on a number of subjects we were able to obtain fairly complete figures concerning daily plasma level and urinary excretion, hence it was possible to place the day on which excretion over 40 mg first occurred and the first day of excretion of 50 per cent of the ingested dose. The use of 40 mg every twenty-four hours as a measure of normal excretion is arbitrary. In our present series, from examination of the data on fractionated specimens, we

2 Roe, J. H., and Kuether, C. A. The Determinations of Ascorbic Acid in Whole Blood and Urine Through the 2,4-Dinitrophenylhydrazine Derivative of Dehydroascorbic Acid, *J Biol Chem* **147** 399 (Feb) 1943.

3 Mindlin, R. L., and Butler, A. M. The Determination of Ascorbic Acid in Plasma. A Macromethod and a Micromethod, *J Biol Chem* **122** 673 (Feb) 1938.

4 van Eekelen, M., and Heinemann, M. Critical Remarks on the Determination of Urinary Ascorbic Acid, *J Clin Investigation* **17** 293 (May) 1938.

noted that to reach an excretion level above 40 mg every twenty-four hours usually 75 per cent or more of the total saturation dose was needed. Published data on normal excretion or usual excretion with a normal diet give figures rang-

ing from 13 to 35 mg every twenty-four hours.⁵ Until recently the methods for assaying urinary content of vitamin C measured the reduced ascorbic acid only, while our values for excreted vitamin C represent the total ascorbic acid in

TABLE 2—Results of Daily Doses of Ascorbic Acid in Twenty-Seven Patients

Subject	Basic Levels		Supplemented Levels				Sex	Age	Diagnosis
	Plasma, Mg per 100 Cc	Excretion 24 Hours, Mg	Daily Dose, Mg	Administration	Plasma, Mg per 100 Cc	Excretion 24 Hours, Mg			
1	0.62	7	100 100	Oral Oral	0.59 0.52	6 7	I	31	Psychoneurosis
2	0		200 200 6 days	Oral Oral	0.03 1.53	1 70	M	72	Parkinson's disease, arteriosclerosis, duodenal diverticulum
3	0	2	500 500	I V* I V	0 0	5 8	M	63	Carcinomatosis, arteriosclerotic kidneys
4	0.20	11	500 500 500	Oral Oral Oral	0.47 0.92 1.12	13 32 251	M	45	Hyperparathyroidism, generalized vitamin deficiencies
5	0.10	7	500 500 1 day 500 6 days	Oral Oral Oral	1.37 1.10	7 29 214	I	15	Bronchial asthma, ovarian hypofunction
6	0.10		500	Oral	0.30	7	M	39	Hypertensive heart disease with reduced renal function
7	0	2	600 600	I V I V	0 0	20 29			
7	0.05	11	600 600 600 600	Oral Oral Oral Oral	0.19 0.46 0.79 1.28	11 68 112 207	M	38	Hypertensive cardiorenal disease
8	0.24		600	Oral	0.83	11	M	51	Gastric carcinoma
9	0.25		600	Oral	0.87	39	M	62	Gastric carcinoma
10	0		600	Oral	0.65	11	M	72	Gastric ulcer
11	0.01	6	600 600 4 days	Oral Oral	0.71 0.65	10 354	F	21	Scurvy with arthritis
12	0.13	1	(400) 500 500	Oral Oral Oral		(4) 1 186	M	17	Spastic bowel, migraine, pyorrhea
13	0.39		500	Oral	0.90	13	M	71	Hypertrophic arthritis, arteriosclerosis
14	0.36		500	Oral	1.11	351	M	72	Rheumatoid arthritis
15	0.15		500	Oral	0.71	10	M	13	Malnutrition, psychoneurosis
16	0	4	500 2 days 500	Oral Oral	0.11 0.91	6 1	M	11	Gastric ulcer
17	0.13		500	Oral	0.88	4	M	29	Neurocirculatory asthenia
18	0.05	5	500 2 days 500	Oral Oral	0.29 0.52	2 1	M	20	Ulcerative colitis
19	0		1 Gm 1 Gm 1 Gm 1 Gm	I V Oral Oral Oral	0 0 0 0.08	15 8 14 6	M	36	Myelogenous leukemia
20	0		1.5 Gm	I V	0.62	134	M	56	Ulcerative colitis, slightly reduced kidney function
21	0		1.5 Gm	I V	0	131	M	46	Hodgkin's sarcoma, suggested renal damage
22	0.27		1.5 Gm	I V	1.50	552	M	66	Nonmalignant cyst of tongue
23	0.21		1.5 Gm	Oral	1.49	82	M	45	Recurrent duodenal ulcer
24	0.10		1.5 Gm	Oral	1.35	118	M	57	Arteriosclerotic heart failure, duodenal ulcer, pyorrhea
25	0		1.5 Gm	I V	0	35			
25		7		Data incomplete			M	45	Anxiety state with vomiting
26	0	4		Data incomplete			M	54	Duodenal ulcer, extrarenal uremia due to alkali therapy
27	0.11			Data incomplete			M	62	Chronic lymphogenous leukemia, renal damage

* I V indicates intravenous injections of sodium ascorbate

5 (a) Hawley, E. E., Stephens, D. J., and Anderson, G. The Excretion of Vitamin C in Normal Individuals Following a Comparable Quantitative Administration in the Form of Orange Juice, *Cevitamic Acid by Mouth and Cevitamic Acid Intravenously*, *J. Nutrition* **11** 135 (Feb.) 1936. (b) Finkle, P. Vitamin C Saturation Levels in the Body in Normal Subjects and in Various Pathological Conditions, *J. Clin.*

Investigation **16** 587 (July) 1937. (c) Rall, E. P., Friedman, G. J., and Sherry, S. Vitamin C Requirement in Man Estimated After Prolonged Studies of the Plasma Concentration and Daily Excretion of Vitamin C in Three Adults on Controlled Diets, *ibid* **18** 705 (Nov.) 1939. (d) Brown, A. P., Fincke, M. L., Richardson, J. E., Todhunter, E. N., and Woods, E. Ascorbic Acid Nutrition of Some College Students, *J. Nutrition* **25** 411 (May) 1943.

the urine, that is, the reduced plus the dehydroascorbic acid Berryman and others⁶ found that dehydroascorbic acid averaged 18 per cent of the total amount excreted It is generally understood that saturation is indicated by excretion of 50 per cent of the administered dose

For 20 subjects (table 3) we have sufficient data to obtain information regarding the amount

TABLE 3—The Renal Threshold for Ascorbic Acid

Subject	Plasma, Mg per 100 Cc				Cumulative Dosage of Ascorbic Acid, Gm	
	Basic	After Treatment But Before Spill	On 1st Day of Excretion Over 40 Mg	Day of Excretion of 50% of Dose	On 1st Day of Excretion Over 40 Mg	Day of Excretion of 50% of Dose
8	0.24	0.83	1.91	1.91	1.5	1.5
12	0.13		1.67	1.74	2.0	2.8
13	0.39	0.90	1.43	1.43	2.0	2.0
24	0.10		1.35		1.5	
14	0.36		1.11	1.12	0.8	2.0
25	0.02		0.26		0.5	
23	0.24		1.49		1.5	2.0
1	0.62	0.52	1.50		0.5	
7	0.05	0.19	0.46	1.28	0.6	2.4
2	0	0.96	1.53	1.42	1.2	1.4
10	0	0.65	1.51	1.51	1.5	1.5
22	0.27		1.50		1.5	
4	0.20	0.92		1.12	0.9	1.5
11	0.04	0.74	0.67	0.67	1.8	1.8
5	0.10	1.37	1.50	1.40	1.5	1.8
16	0	0.91	Not reached		Not reached	
9	0.25	0.87	1.34		1.5	
17	0.13	0.88	1.40	1.40	2.0	2.0
6	0.10	0.30	0.63	0.60	1.5	2.5
20	0		0.62		1.5	

of ascorbic acid needed to bring the excretion of vitamin C to normal and saturation levels It will be noted that in many cases the subject's plasma level is fairly high before the excretion has reached 40 mg Subjects who reached the saturation point within twenty-four hours had, of course, no reading between the basic and saturation levels In 15 subjects the plasma level was over 1.0 mg per hundred cubic centimeters at the time the excretion reached 40 mg Of the 5 exceptions, it may be noted in table 2, 4 suffered disturbed or damaged renal function The condition of the fifth was diagnosed as scurvy with arthritis It is not known that scurvy affects the renal tubules so as to lower the ascorbic acid threshold Russel and Calloway,⁷

6 Berryman, G. H., French, C. E., Harper, H. A., and Pollack, H. Response to the Intravenous Injection of Ascorbic Acid as Indicated by the Urinary Excretion of the Total and Reduced Forms, *J. Nutrition* 27:309 (April) 1944

7 Russel, W. O., and Calloway, C. P. Pathologic Changes in the Liver and Kidneys of Guinea Pigs Deficient in Vitamin C, *Arch. Path.* 35:546 (April) 1943

in a report of experiments on guinea pigs, described changes in the cytoplasm of the cells of the convoluted proximal tubules in the scorbutic animals and conclude that vitamin C deficiency produces a pathologic change in the cells of the kidney Since scurvy does cause deterioration of the supporting tissues throughout the body and apparently alters the structure of the capillary wall very early, it is possible that the effect on the renal tubules may be to increase permeability to ascorbic acid

Aside from the (apparently) pathologic renal threshold described in 5 of our cases, the data in table 3 suggest that the threshold for ascorbic acid may vary between 1.12 and 1.91 mg per hundred cubic centimeters in 10 patients In 5 additional patients, who had not really reached the saturation point it is evident that the threshold is not lower than 1.34

TABLE 4—Effects of Administration of Ascorbic Acid on Plasma and on Whole Blood

Subject	Day	Plasma, Mg per 100 Cc	Whole Blood, Mg per 100 Cc	Cumulative Dose, Gm
12	Basic	0.13	0.20	
	3	1.67	1.47	2.0
	4	1.74	1.66	2.8
19	B	0.00		
	1	0.00		1.5
	2	0.00	0.76	2.5
	3			3.5
	4			4.5
	5	0.08	0.51	5.5
	6	0.00	0.39	6.5
25	B	0.02	0.35	
	1	0.26	0.58	0.5
	2	0.79	0.86	1.0
3	B	0.00	0.06	
	1	0.00	0.09	0.3 (IV)
	2	0.00	0.15	0.6
	3		0.23	1.2
	4		0.38	1.8
	5	0.34	0.72	2.4
	6	0.63	0.90	3.4
2	7	0.36	0.74	3.4
	B	0.00		
	6	1.53	1.68	1.2
21	7	1.42	1.77	1.4
	B	0.00	0.12	
	1	0.00	0.46	1.5
M D	2	0.37	0.51	2.5
	B	0.69		
M B	1	0.55	0.69	0.1
	B	1.10		
4		1.40	1.48	0.4

Some data on comparisons of whole blood and plasma are given in table 4 Readings were made on the same blood sample in each case Most of the observations were made on the subjects of this series in connection with excretion studies, but a few additional ones are from normal subjects obtained at various times throughout the past year

It still appears, from what we have observed, that whole blood is no more valuable than plasma in estimating the patient's need for vitamin C therapy. In the low ranges, which are of concern to the diagnostician, the whole blood level of ascorbic acid was higher than its plasma level, but the greatest difference found was 0.12 mg per hundred cubic centimeters, except only in the case of subject 25, who had been receiving a high alkali intake, from which evident disturbance of renal function had occurred. It is known that vitamin C is destroyed by alkali, and the fact that at the time of the first blood sample alkali therapy had not been stopped suggests the possibility of destruction of vitamin C in the plasma out of proportion to destruction of that in the cells. Furthermore, it will be noted that on the third day after cessation of therapy

TABLE 5—*Ascorbic Acid Levels in Plasma Compared with Those in Whole Blood*

Plasma Levels 0.0 to 0.16 Mg /100 Cc			Plasma Levels Over 1.0 Mg /100 Cc			Plasma Levels Over 1.0 Mg /100 Cc		
Whole Plasma	Differ Blood	ence	Whole Plasma	Differ Blood	ence	Whole Plasma	Differ Blood	ence
0.00	0.06	0.06	1.05	1.17	0.12	1.42	1.77	0.35
0.00	0.08	0.08	1.12	1.20	0.08	1.53	1.68	0.15
0.00	0.09	0.09	1.30	1.36	0.06	1.67	1.47	-0.20
0.06	0.18	0.12	1.40	1.48	0.08	1.74	1.66	-0.08
0.08	0.13	0.05	Range 0.06 to 0.12			1.77	1.98	0.21
0.08	0.13	0.05				Range 0.08 to 0.35		
0.13	0.20	0.07						
0.16	0.23	0.07						
Range 0.05 to 0.12								

(table 4) the divergence of 0.33 was decreased to 0.07 mg per hundred cubic centimeters, a figure which is in line with the others.

In making the comparison of whole blood level and plasma level for values above 1.0 mg we included some normal persons. We have seen no normal persons with values in the low ranges just discussed. The remainder of the comparisons are made on samples from patients after treatment with ascorbic acid. In four pairs the greatest divergence was 0.12, the same as for the low group. Five pairs in which all values were above 1.40 mg showed a divergence from 0.08 to 0.35, and in two of these samples the plasma value was higher than that of the whole blood. In none of the others was the plasma higher than the whole blood. Further study in this field is contemplated to allow us to investigate the relationship between whole blood and plasma, especially at threshold levels. It may be that blood cells will carry higher concentrations of vitamin C than the plasma until a point—perhaps 1.4 mg or over—is reached, after

which an equilibrium seems to be established. It becomes increasingly difficult to increase the cell concentration of ascorbic acid by greater forced intake of vitamin C. Faulkner and Taylor⁸ have previously reached the conclusion that ascorbic acid is a threshold substance with a critical level of excretion in the vicinity of 1.40 mg per hundred cubic centimeters of plasma, and Heinemann⁹ stated that rapid excretion by the kidneys takes place when the serum level of vitamin C passes 1.40 mg. While supplements were being administered to deficient subjects, it may be noted that (table 4) the relationship between whole blood and plasma was considerably altered.

Included in table 4 is 1 case of myelogenous leukemia (no. 19) in which the plasma level remained zero or nearly so throughout six days while 6.5 Gm of ascorbic acid was administered. The whole blood level was not obtained until after 2.5 Gm had been received intravenously, at which time it reached the highest value recorded. Although the treatment was continued, the level dropped appreciably. Loss by excretion was not a factor, as the figures show. High voltage roentgen ray therapy to the spleen was applied daily, and toward the end of the period the drop in the white cell count was great. This may account for the decrease in whole blood content of vitamin C, since the white cells contain a greater concentration of vitamin C than any of the other constituents of the blood. However, the problem posed by the disappearance of these enormous doses of ascorbic acid can be answered only by the assumption that the administered vitamin is destroyed. In cases such as these, plasma studies are obviously inadequate, and the problem must be attacked from several angles. Butler and Cushman have published some data on the subject.¹⁰ It is felt that study of the white cell and platelet layer of the blood will furnish more information than studies of the whole blood. Until an adequate number of cases are studied and the effects of roentgen ray therapy carefully scrutinized, it is useless to theorize.

FACTORS INFLUENCING INDIVIDUAL REQUIREMENTS OF VITAMIN C

The amount of vitamin C needed to prevent signs of deficiency or to restore deficient levels

8 Faulkner, J. M., and Taylor, F. H. L. Observations on the Renal Threshold for Ascorbic Acid in Men, *J. Clin. Investigation* **17**: 69 (Jan.) 1938.

9 Heinemann, M. Distribution of Ascorbic Acid Between Cells and Serum of Human Blood, *J. Clin. Investigation* **20**: 39 (Jan.) 1941.

to normal levels appears to be little affected by a variation in age in men between the ages of 20 and 75. There seems to be some evidence of effects of sex variation. Our observations on women are limited but tend to corroborate Mickelsen's¹⁰ data which indicate fluctuations in plasma content of ascorbic acid corresponding to certain phases in the menstrual cycle. This suggestion of a relation between vitamin C and estrogens is not a new idea. Among others, Selkurt and associates,¹¹ on the basis of experimentation with animals (dogs), made the statement that "estradiol benzoate increases the clearance of ascorbic acid by reducing tubular reabsorption so that the rate of excretion is increased while the plasma level tends to be reduced." They noted that in the normal dog tubular reabsorption of ascorbic acid is incomplete at plasma levels considerably below those required to effect complete saturation of the tubules, consequently ascorbic acid is excreted in the urine at all plasma levels. In the course of treatment with estradiol benzoate, it was necessary to increase the load level of ascorbic acid considerably in order to produce a maximal reabsorption equivalent to the normal.

As it was previously pointed out, certain diseases apparently affect the efficiency of the body in handling administered ascorbic acid. Renal damage or disturbance in every instance impaired the efficiency, especially with the larger doses. While the effect in our cases seems to be a lowered renal threshold for ascorbic acid, the opposite effect has been observed in other kinds of renal damage.¹² An altered response to therapy was noted in conditions of leukemia, Hodgkin's sarcoma and scurvy.

10 Mickelsen, O., Dippel, A. L., and Todd, R. L. Plasma Levels in Women During the Menstrual Cycle, *J. Clin. Endocrinol.* **3**: 600 (Nov.) 1943.

11 Selkurt, E. E., Talbot, L. J., and Houck, C. R. The Effect of the Administration of Estrogen on the Mechanism of Ascorbic Acid Excretion in the Dog, *Am. J. Physiol.* **140**: 260 (Nov.) 1943.

12 Sendroy, J., and Miller, B. F. Renal Function as a Factor in the Urinary Excretion of Ascorbic Acid, *J. Clin. Investigation* **18**: 135 (Jan.) 1939.

SUMMARY AND CONCLUSIONS

The effects of large doses of synthetic ascorbic acid on urinary excretion, plasma and whole blood were studied in patients hospitalized for other ailments but judged to be also deficient in vitamin C on the basis of history, clinical signs and low plasma content of ascorbic acid. The results of this study showed that:

1 The efficiency of single doses of ascorbic acid of 100 to 500 mg. was excellent if the plasma level of ascorbic acid was low.

2 Some patients received as much as 1.5 Gm. of ascorbic acid in one day without significant urinary loss, while the plasma content of vitamin C was increased to high normal levels.

3 The total amount of ascorbic acid supplement required to produce a twenty-four hour excretion of 40 mg. or over varied from 0.5 to 2.0 Gm. and the amount required for saturation, from 1.5 to 2.8 Gm.

4 Intravenous administration of ascorbic acid resulted in slightly greater excretion in a few cases.

5 A wide individual variation in the renal threshold for ascorbic acid is strongly indicated, the probable plasma level for this series being between 1.1 and 1.9 mg. per hundred cubic centimeters.

6 It was not demonstrated that a determination of the whole blood level is superior to that of the plasma level in diagnosing vitamin C deficiency. Patients with low plasma values generally excreted very small amounts of ascorbic acid until dosage had raised the plasma levels above 1.0 mg.

7 Disease appears to be one factor that may influence the response to ascorbic acid treatment. Patients having renal involvement or blood dyscrasias responded atypically.

8 Age did not appear to affect the results significantly.

9 Variations that may be attributed to sex differences occurred in the results of ascorbic acid treatment in these patients.

PRIMARY SYSTEMIC AMYLOIDOSIS OF THE ALIMENTARY TRACT

ABNER GOLDEN, M D

ATLANTA, GA

Primary systemic amyloidosis is a rare disease. It occurs in the absence of predisposing diseases and is characterized by deposition of amyloid chiefly in the tongue, the alimentary tract and the heart. Koletsky and Stecher¹ recently reviewed 24 cases of this disease reported in the American and foreign literature and added 2 cases of their own. Two additional cases have since been reported.²

The following case involved an example of this disease with primary involvement of the alimentary tract, it presents several unusual features.

REPORT OF A CASE

M T, a 66 year old Negress, was admitted to the medical service of the Grady Hospital in July 1943, with the chief complaint of massive hematemesis three hours before admission.

History—The patient had been seen frequently in the outpatient clinic since 1927, when she came to the hospital because of constipation and poor appetite. At that time she appeared underweight. Her blood pressure was 160 systolic and 114 diastolic. Her symptoms failed to respond to therapy. She first noted a sensation of "fulness" in the epigastrium in 1931, and in 1940 she had frequent attacks of epigastric pain, which were relieved by food. Her symptoms were progressive. A series of gastrointestinal examinations in 1933 showed no pathologic changes, and a study of the gallbladder in 1941 gave results which were interpreted as normal.

For several months prior to her entry into the hospital she had some exertional dyspnea, slight orthopnea and intermittent edema of the ankles. She had occasional dysuria and nocturia, but numerous urinalyses revealed albuminuria of only 1 to 2 plus. Numerous serologic tests for syphilis gave negative results.

One week prior to her entry persistent pain in the lower part of the abdomen developed. She had frequent foul-smelling light yellow stools associated with abdominal cramping. She became progressively weaker. Three hours before her admission severe "drawing" epigastric pain, which radiated to the back, developed, and she vomited about a pint of "coffee-ground" material with flecks of fresh blood.

Physical Examination—The patient was a weak, emaciated Negress. Her temperature was 99.6 F, her pulse rate 112, her respiratory rate 14 and her blood pressure 200 systolic and 110 diastolic. An indefinite,

soft, tender mass was palpated in the midepigastrium. There was no muscular spasm, and peristalsis was present. The apex impulse of the heart was located 11 cm to the left in the fifth intercostal space. The rhythm was regular, except for occasional premature contractions. There was slight pitting edema of the legs. The lungs were clear. The skin over the forearms was dry and scaly. The tongue was bright red and glossy. There were no other significant observations.

Laboratory Data—Frequent urinalyses showed a specific gravity of 1.004 to 1.014 and albuminuria, 2 to 4 plus. The urinary sediment contained occasional white blood cells and rare granular casts. The red blood cell count was 4,300,000 per cubic millimeter, and the hemoglobin content of the blood was 9 Gm per hundred cubic centimeters. The sedimentation rate on two occasions was 14 and 45 mm respectively per hour. The white blood cell count was 6,550 per cubic millimeter, with a normal differential count. Subsequent white cell counts varied between 4,500 and 9,000. The icterus index was 10. The plasma protein level was 7.3 Gm per hundred cubic centimeters, later falling to 3.9 per hundred cubic centimeters. Examinations of stools gave positive results for blood for several days after her admission but then gave negative results. The non-protein nitrogen on two occasions was 25 and 27 mg per hundred cubic centimeters. A phenolsulfonphthalein test showed excretion of 67.5 per cent of the dye in two hours. A gastric analysis showed no free acid after the administration of histamine phosphate.

A series of gastrointestinal examinations showed a constant irregular narrowing of the pyloric antrum and a large duodenal cap measuring 7 by 7 cm. There was 50 per cent gastric retention after six hours. Roentgen examination after a barium sulfate enema showed no obstruction in the large intestine.

Course in the Hospital—The patient was put on a Sippy regimen but continued to complain of epigastric and abdominal pain. After administration of barium by mouth marked intestinal hypotonia and fecal impaction developed, which were only partially relieved by vigorous measures. She persistently vomited everything taken by mouth.

The patient was transferred to the surgical service, where a laparotomy was performed. A bizarre, white, marble-like discoloration of the entire stomach and of the large and small intestines was found. It appeared to follow the longitudinal muscle fibers of the wall of the bowel and did not involve the mesentery. A mass was palpable in the greater curvature of the stomach, in the prepyloric region. Approximately three fourths of the stomach was removed by the Hofmeister technic.

Postoperatively the patient did poorly. She was unable to retain food. Fecal impaction again developed, and a cecostomy was performed nine days later. Despite all therapy her course continued down hill, and she died on her sixty-ninth day in the hospital.

From the Departments of Pathology of Grady Memorial Hospital and Emory University School of Medicine.

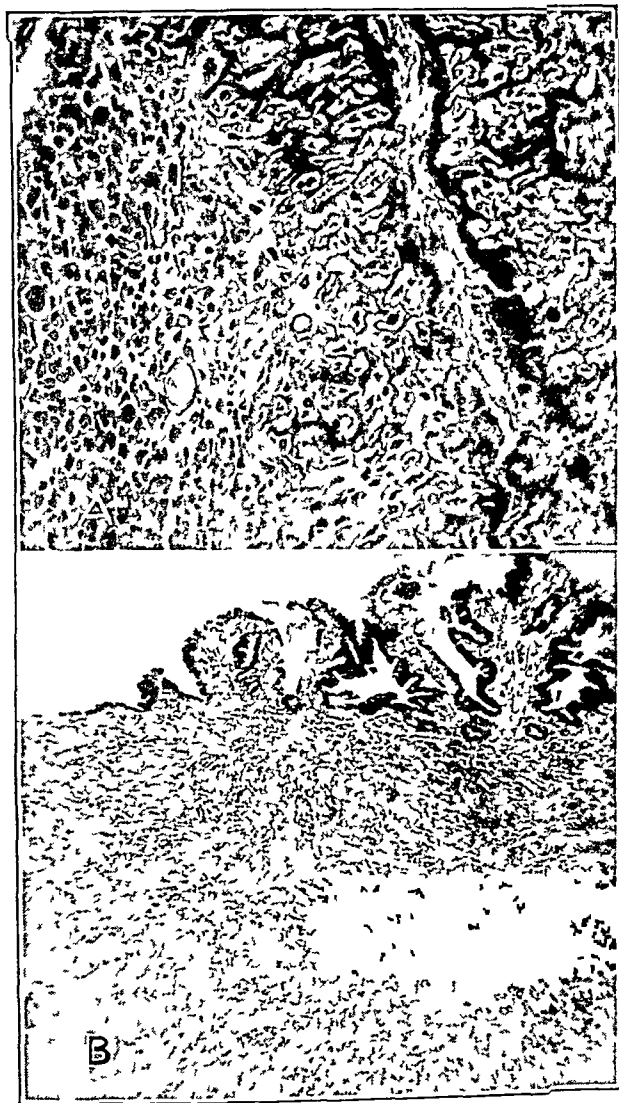
1 Koletsky, S, and Stecher, R M. Primary Systemic Amyloidosis, Arch Path **27** 267 (Feb) 1939.

2 Pearson, B, Rice, M M, and Dickens, K L. Primary Systemic Amyloidosis, Arch Path **32** 1 (July) 1941.

An intravenous congo red test was performed three days before death. Sixty-five per cent of the dye was retained in the blood after one hour.

Morphologic Observations on Surgical Specimen—GROSS OBSERVATIONS—On examination the serosa of the stomach was seen to consist of smooth, grayish white, glistening tissue, extending 2 to 3 mm into the wall. When the stomach was opened, two superficial ulcerations of the mucosa, 1 and 1.5 cm respectively in diameter, were found along the greater curvature, near the pylorus. The surrounding tissue was elevated but not indurated.

HISTOLOGIC OBSERVATIONS—Sections of the stomach were stained with phloxine-methylene blue, hematoxylin and eosin, congo red, crystal violet and iodine.



A, the muscular coat of the stomach. There is an increase of interstitial tissue caused by deposition of amyloid with resulting atrophy of muscle fibers. In this field the process varies from slight to fairly advanced in degree. Phloxine-methylene blue, $\times 400$. *B*, gastric ulcer. There are marked fibrosis and inflammatory cell infiltration of the muscularis mucosae and the submucosa. The mucosa shows some repair. Hematoxylin-eosin, $\times 40$.

Extensive and almost continuous amyloid deposits were found in the outer layers of the muscular coat and extending inward. They had caused atrophy and replacement of the greater portion of the musculature (fig. *A*). Less extensive patchy areas of amyloid de-

posits involved the distinctly hypertrophic muscularis mucosae. Other slight amyloid deposits were seen within the walls of the blood vessels, chiefly at the bases of the ulcerations. These ulcerations involved the muscularis mucosa but did not extend beyond it (fig. *B*). Their fundi and the adjacent tissue were heavily infiltrated by chronic inflammatory cells. Fibrosis of long standing was seen surrounding the ulcerations, and within this scar tissue a large number of partially or completely obliterated blood vessels were seen. The mucosa at the margin of the ulcers showed varying degrees of regeneration but no evidence of anaplasia. In the remaining portions of the stomach the mucosa showed considerable chronic inflammatory cell infiltration.

DIAGNOSIS—The diagnosis was amyloidosis of the stomach and two prepyloric ulcers.

Report of Autopsy—Gross Observations. An autopsy was performed six hours after death. Permission was not granted for examination of the head. The body was fairly well developed but poorly nourished. There was pitting edema of the lower extremities. The operative incisions were in a poor state of healing.

When the peritoneal cavity was opened, the entire intestinal tract appeared bright red because of the extensive deposition of congo red dye. The remaining portion of the stomach, the duodenum and the terminal portion of the ileum showed extensive and diffuse involvement. The esophagus and the remaining portion of the intestinal tract, including the appendix, showed extensive but patchy deposits. The intestinal wall felt thickened and waxy. There were a few hemorrhages in the wall of the small intestine. Hemorrhages were more numerous in the wall of the descending colon. A sharp obstructing kink was found in the jejunum just distal to the gastrojejunal anastomosis, which was in good condition. The peritoneal cavity contained 1,000 cc of clear yellow fluid. Localized peritonitis was present in the region of the abdominal incision. When the alimentary tract was opened, it was seen that the deposits of congo red were confined to the muscular coat and the muscularis mucosae. The mucosa throughout appeared normal, and no ulcerations were seen.

The heart weighed 290 Gm. Scattered throughout the endocardium, chiefly in the left auricle, were numerous small deposits of congo red, each 3 to 4 mm across. Numerous small firm red nodules, 0.5 to 1 mm in diameter, were present on the cusps and the annulus fibrosus of the mitral and tricuspid valves. A few small deposits were also seen in the proximal portion of the pulmonary artery. No other significant features were noted in the heart.

The spleen weighed 25 Gm. Its surface was firm and granular. The cut surfaces were deep purple, and the trabeculae were prominent.

No deposits of congo red were grossly visible in the liver, the spleen, the kidneys or the adrenal glands. A few deposits were noted in the splenic artery.

Other observations included pulmonary congestion, a moderately advanced degree of arteriosclerosis and chronic cholecystitis. No foci of tuberculosis or chronic suppuration were encountered.

Histologic Observations. Tissues were fixed in Zenker's fluid with 5 per cent acetic acid and in solution of formaldehyde (10 per cent concentration). U. S. P. The following stains were employed: phloxine-methylene blue and aniline blue routinely, congo red, Mayer's crystal violet-iodine reaction, Herxheimer's scarlet red and Turnbull's stain for iron on selected sections.

The heart showed numerous patchy areas of old scarring, with large deposits of amyloid. In these areas

there was atrophy of the myocardial muscular bundles without evidence of acute necrosis. These areas were most frequently encountered near the endocardial surface. In the auricles a large proportion of the musculature appeared to have been replaced by amyloid. A relationship between these lesions and extensive deposits of amyloid in the small arteries and arterioles was strongly suggested. Large deposits of amyloid were seen in the cusp and the annulus fibrosus of the mitral valve, which was otherwise normal.

The lungs showed early bronchopneumonia, edema and slight atelectasis and emphysema.

The spleen contained no amyloid. The red pulp was congested and showed some phagocytosis of the erythrocytes. An iron stain showed considerable accumulation of iron pigment within large mononuclear cells.

Extensive amyloid deposits were seen in the esophagus, the small and large intestines and the appendix. The process was almost entirely limited to the muscularis, with patchy involvement of the muscularis mucosae. The outer longitudinal musculature was constantly involved, the inner circular layer less frequently. In many areas the sequence of events could be traced in the patchy and later often confluent deposition of amyloid in the interstitial connective tissue, with subsequent atrophy of muscle fibers. There was no evidence of acute necrosis. Although many small arteries and arterioles contained medial deposits of amyloid, no definite relationship between these vessels and the diffuse interstitial deposits could be demonstrated.

In the pancreas some small amyloid deposits were seen in the walls of several small arteries and arterioles and in some of the small veins.

The liver showed marked congestion and fatty degeneration. Small deposits of amyloid were present in some of the branches of the hepatic artery, but no other amyloid was seen.

The kidneys showed peculiar tubular lesions, characterized by marked vacuolation of the epithelial cells of the distal convoluted tubules. These did not contain fat. There was moderate arteriosclerosis. No amyloid was present.

The adrenal glands were not remarkable except for some amyloid in several small arteries and in one large medullary vein.

The aorta displayed a moderate degree of arteriosclerosis. No amyloid was seen. The gallbladder showed some old scarring. No significant features were noted in the other organs, including the skeletal muscle, the bone marrow and the spinal cord.

The amyloid deposits described stained well with congo red, weakly with crystal and gentian violet and not at all with iodine.

Anatomic Diagnosis The following diagnoses were made: primary amyloidosis of the esophagus, stomach, intestinal tract and heart and of the arteries of the pancreas, liver and adrenal glands, intestinal obstruction, ascites (1,000 cc), recent subtotal gastrectomy, recent colostomy, localized peritonitis, early bronchopneumonia, pulmonary edema, congestion of the viscera, generalized arteriosclerosis, inactive chronic cholecystitis, emaciation.

COMMENT

Causation—The causation of amyloid disease remains obscure. It appears to be a disease primarily of connective tissue. It can be reproduced in animals, principally the horse and the rabbit. In these animals the appearance of amyloid deposits is associated with a rise in

the serum globulin.³ Although usually the disease in human beings is not accompanied by demonstrable changes in the serum proteins, there is a more than coincidental association of amyloid disease with multiple myeloma, in which high globulin fractions are common. It has been suggested that deposition of amyloid substance results from a reaction of fixed tissue elements with a fraction of the serum globulin, perhaps on an allergic basis.¹

This hypothesis receives support from the work of Hass and associates.⁴ By fractionation of amyloid, a protein was found which was soluble between p_H 11 and p_H 12. The specific solubility appeared to be determined by a sulfate-bearing polysaccharide similar in properties to chondroitin-sulfuric acid. Different solubility properties were found in the amyloid of rabbits inoculated with tuberculin, horses receiving large doses of tetanus and human beings. Furthermore, differences were found in the amyloid in persons with tuberculosis and in persons with chronic osteomyelitis, as well as in animals under different causative circumstances. It was concluded that the properties of amyloid depend not only on the species but on the method of cause of production.

Types—Human amyloid disease has been divided into four types: secondary amyloidosis, primary amyloidosis, amyloidosis associated with multiple myeloma and localized amyloid tumors.

Secondary amyloidosis occurs during the course of many chronic debilitating diseases, the most common being tuberculosis and chronic suppuration. The organs characteristically involved are the liver, the spleen, the kidneys and the adrenal glands, although small deposits may be found in any organ of the body. The amyloid deposits are usually clearly vascular and perivascular in distribution and generally stain well with congo red, crystal violet and iodine. In advanced stages the intravenous congo red test gives uniformly positive results.

Primary systemic amyloidosis occurs in the absence of predisposing diseases. The organs most frequently involved are the tongue, the

3 Reimann, H. A., and Eklund, C. M. Long-Continued Vaccine Therapy as a Cause of Amyloidosis, *Am J M Sc* **190** 88 (July) 1935. Dick, G. F., and Leiter, L. Experimental Amyloidosis and Hyperglobulinemia, *Tr A Am Physicians* **52** 246, 1937. Reitstetter, J. Ueber die Goldzahl von normalem und pathologisch verändertem Blutserum, *Ztschr f Immunitätsforsch u exper Therap* **30** 468, 1920.

4 Hass, G. M. Studies of Amyloid. II. The Isolation of a Polysaccharide from Amyloid-Bearing Tissues, *Arch Path* **34** 92 (July) 1942. Hass, G. M., Huntington, R., and Krundieck, N. Amyloid. III. The Properties of Amyloid Deposits Occurring in Several Species Under Diverse Conditions, *ibid* **35** 226 (Feb) 1943.

heart, the stomach, the intestines, the skeletal muscles and the skin. Extensive deposits in the joints, tendons, bones, larynx, trachea, bladder and genitalia have also been reported. The liver, spleen, kidneys and adrenal glands usually contain little amyloid. The symptomatology depends on the organs involved. The average duration of the disease is two to three years, although in 1 case¹ it apparently persisted for fourteen years.

In most of the reported cases the amyloid deposits gave varying reactions with the usual specific staining technic, although positive reactions were obtained with at least one of the stains. Varying results were also obtained with the intravenous congo red test, many patients showing normal retention of the dye in the blood.

Amyloidosis associated with multiple myeloma is similar in distribution and staining characteristics to primary amyloidosis.

Localized amyloid tumors are occasionally seen in the larynx, tongue, eye, bladder and bones. They are usually solitary but may be multiple.

The case here reported seems to fill the necessary criteria for the diagnosis of primary systemic amyloidosis. The involvement was chiefly gastrointestinal, and there was moderate deposition in the myocardium and in the tricuspid and mitral valves. The parenchyma of the liver, spleen, kidneys and adrenal glands contained no amyloid. No foci of tuberculosis or chronic suppuration were encountered.

Points of Special Interest—Several points are of special interest. Two ulcerations of the gastric mucosa were found in the operative specimen. These were obviously of long standing, and may account for the patient's chief

complaint. Gastric ulcers have been reported in but 1 other case of primary amyloidosis.⁵ Here, too, hematemesis had occurred. The involvement of the heart valves seen in this case has been reported but twice before.² The intravenous congo red test, performed shortly before death, showed a normal retention of dye in the blood after one hour. This is in keeping with the observations of other authors.¹ The vital staining of all amyloid deposits in the body afforded by this intravenous test is perhaps unique in this case. The failure of the amyloid deposits to stain well with crystal violet and iodine is also in keeping with previous experience with this disease.

Of interest, also, is the long history of gastrointestinal complaints of this patient, dating back sixteen years before death. It seems reasonable to assume that the terminal intestinal hypotonia was due to massive replacement of the intestinal musculature by amyloid, but the relation of amyloid deposition to the patient's early symptoms cannot be determined.

SUMMARY

In a case of primary systemic amyloidosis with involvement chiefly of the alimentary tract the presenting clinical symptoms were those of gastric ulcer.

Intravital staining of the amyloid deposits following an intravenous congo red test, involvement of the heart valves and presence of gastric ulcerations are the unusual features of this case.

⁵ Lubarsch, O. Zur Kenntnis ungewöhnlicher Amyloidablagerungen, *Virchows Arch f path Anat* 271 867, 1929.

Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM JULY 1943 TO JUNE 1944

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(Concluded from page 356)

COLON

Physiology—Sheehan,⁴⁰⁶ in discussing the effect of the autonomic nervous system on the physiologic functions of the gastrointestinal tract, considers the sympathetic and vagotonic manifestations as not distinctly separable but as called into play simultaneously in a selective manner. These manifestations may be either homeostatic or an expression of emotional behavior. When the autonomic response becomes excessive, symptoms result.

Krost⁴⁰⁷ reports 2 fatal cases of generalized atony of the whole gastrointestinal tract in newborn infants, the condition was attributed to an unproved imbalance of the autonomic nervous system.

Mayoral⁴⁰⁸ presents a case of tumor in the hypothalamic region in which "altered motility of the colon was observed fluoroscopically one month and eight days previous to death." The contractions were forceful and complete. The motor disturbance was attributed to the tumor.

Galambos,⁴⁰⁹ in discussing the motility of the colon, presents a roentgenologic study of the large pendulum movement, with the conclusion that while it is not a regular physiologic process it is not necessarily abnormal. Redundancy and a long mesentery are necessary prerequisites. Hence volvulus and invagination may occur.

A comparative experimental and clinical study was made by Necheles and associates⁴¹⁰ of both

the well known and the newer spasmolytic drugs: atropine sulfate, opium, belladonna, papaverine hydrochloride, methylbiscyclohexylethylamine hydrochloride, tropic acid diethylaminoethyl-propionylbenzylalcohol hydrochloride, amyl nitrite, nitroglycerine, oil of peppermint, diphenylacetyldiethylaminoethanol and hexenyl-phenylacetyldiethylaminoethanol. Atropine and diphenylacetyldiethylaminoethanol were considered to be the most effective in the control of gastrointestinal symptoms. A similar study was made by Ingelfinger.⁴¹¹

In observing a series of 100 laparotomies, in which the patients were treated with neostigmine preoperatively and postoperatively, Koufman⁴¹² found that those treated with neostigmine were more comfortable and had a greatly reduced incidence of intestinal distention.

Rats fed diets containing 10 and 20 per cent additions of lard, cottonseed oil, linseed oil, menhaden oil, Crisco, bayberry tallow, theobroma oil or tributyrin did not have diarrhea—not even when 2 cc doses of castor oil were given by stomach tube.⁴¹³

Wikoff, Gaul and Marks⁴¹⁴ in an excellent study of the effect of the glycerides of the saturated fatty acids on intestinal elimination in the dog, fed measured amounts of pure triglycerides mixed with a standard dog food. Constipation was produced by the feeding of diets containing 20 per cent additions of the triglycerides which

406 Sheehan, D. Physiological Mechanisms Involved in Gastrointestinal Dysfunction, *Psychosom Med* **6** 56-57, 1944

407 Krost, G. N. Autonomic Nervous System Imbalance of the Whole Gastrointestinal Tract in the Newborn Infant, *J Pediat* **24** 635-640, 1944

408 Mayoral, A. Motor Changes Observed Fluoroscopically in the Colon of a Patient Afflicted with a Tumor in the Hypothalamic Region, *Am J Digest Dis* **10** 305-307, 1943

409 Galambos, A. Clinical and Radiological Observations Concerning the Large Pendulum Movement of the Colon, *Am J Digest Dis* **11** 151-158, 1944

410 Necheles, H., Olson, W., Neuwelt, F., and Spier, E. A Pharmacological and Clinical Study of Spasmolytic Drugs, *Gastroenterology* **2** 46-59, 1944

411 Ingelfinger, F. J. The Modification of Intestinal Motility by Drugs, *New England J Med* **229** 114-122, 1943

412 Koufman, W. B. Control of Post-Operative Atonic Intestinal States with Prostigmin, *Mil Surgeon* **93** 187-190, 1943

413 Wikoff, H. L., Koonce, S. D., and McGuire, H. J. Some Effects of High Fat Diets on Intestinal Elimination, *Am J Digest Dis* **10** 266-270, 1943

414 Wikoff, H. L., Gaul, J. F., and Marks, B. H. Some Effects of Diets Rich in the Glycerides of Saturated Fatty Acids on Intestinal Elimination, *Am J Digest Dis* **10** 395-399, 1943

melted above 50 C (tristearin and tripalmitin). The lipid content of the feces was greatly increased, the increase being much greater in neutral fat than in soap fat. The addition of 20 per cent trimyristin (melting point 48 to 50 C uncorrected) did not affect the rate of elimination, although the neutral fat fraction was greatly elevated. The feeding of simple triglycerides of some of the saturated acids containing twelve or less carbon atoms (lauric, capric, caprylic, caproic and butyric acids) produced laxative effects in all cases. The intensity of the action varied inversely with the number of carbon atoms and the melting point of the acid. As the cathartic action of the triglycerides increased, the percentage of added fat that the dogs would eat diminished. All the dogs ate the meals of standard dog food with the addition of 20 per cent trilaurin, but the concentration of added fat had to be reduced in the remainder of the cases. Tributyrin, having the most violent action of any of the fats fed, caused diarrhea in 1 dog when as little as 0.2 per cent was added to the standard food. Furthermore, this dog would not eat all the usual daily ration of a pound (0.5 Kg) of the standard food after the addition of 0.2 per cent tributyrin.

Hurst⁴¹⁵ describes the normal defecation reflex as a mass movement of the feces from the colon into the rectum followed by expulsion due to voluntary contraction evoked by the sensation of a distended rectum. Rectal dyschezia is defined as a disturbance in the normal reflex with the collection of feces in the rectum. Megacolon is a dilatation of the rectum and pelvic colon with feces due to achalasia of the anal sphincter. Hurst advocates gradual rectal dilation as curative treatment. Delano,⁴¹⁶ on the other hand, takes the view that the term rectal dyschezia should be discarded because the rectal retention of feces occurs with and without organic disease and hence does not represent a clinical entity.

Gold and Zahm⁴¹⁷ describe a method for the comparison of laxative agents in constipated human subjects, show that the laxative efficacies of the fumarates of sodium, calcium and magnesium are the same and that these three substances also possess approximately the same

laxative potency as sodium citrate and magnesium acid citrate gram for gram.

Hazelton and Talbert⁴¹⁸ state that the cathartic action of bile salts compound in mice is due to the content of cholic acid, agreeing with the clinical impression that other purified bile salts are not active as cathartics.

Tainter⁴¹⁹ reports that methyl cellulose is a synthetic material having physical and chemical properties suitable for use as a colloid laxative. In doses of 10 Gm it approximately doubled the volume of the stools and increased their frequency. The toxicologic and clinical studies should be extended before its general therapeutic use is approved.

Spiesman⁴²⁰ reviews the history of the rather unsuccessful attempts to change the intestinal flora by using *Bacillus acidophilus*, lactose and dextrin and discusses the use of colloidal kaolin and aluminum hydroxide gel in the treatment of colonic disorders.

Alvarez⁴²¹ analyzes the types of distress commonly due to constipation as well as those produced by strenuous purgation. Ingelfinger⁴²² and Palmer⁴²³ each discuss the syndrome of the "irritable colon." Heilbrun⁴²⁴ presents a case with extensive roentgenographic changes suggesting ileitis and colitis in which the only apparent ascribable cause was the daily use of cathartics for over twenty years.

Roentgenology—Henderson,⁴²⁵ in a well illustrated paper, discusses the technic of the roentgenologic examination of the colon and concludes that the "classic" barium sulfate enema is still the most generally useful method. The use of compression requires careful interpretation, for the observer may be easily misled. The

418 Hazelton, L. W., and Talbert, K. D. Further Studies on Cathartic Action in Mice. Senna, Aloe, Cascara, and Bile Salts, *J Am Pharm A* **33** 170-173, 1944.

419 Tainter, M. L. Methyl Cellulose as a Colloid Laxative, *Proc Soc Exper Biol & Med* **54** 77-79, 1943.

420 Spiesman, M. G. Colloidal-Kaolin and Aluminum-Hydroxide Gel (Kalam*) in the Management of Lower-Bowel Conditions, *Rev Gastroenterol* **10** 191-200, 1943.

421 Alvarez, W. C. Indigestion Due to Constipation, *Gastroenterology* **2** 427-431, 1944.

422 Ingelfinger, F. J. Treatment of the "Irritable Stomach" and the "Irritable Colon," *M Clin North America* **27** 1385-1396, 1943.

423 Palmer, W. L. Functional Disturbances of the Alimentary Tract, *M Clin North America* **28** 418-428, 1944.

424 Heilbrun, N. Roentgen Evidence Suggesting Enterocolitis Associated with Prolonged Cathartic Abuse, *Radiology* **41** 486-491, 1943.

425 Henderson, N. P. The Value of the Opaque Enema and Its Modifications, *Brit J Radiol* **17** 140-149, 1944.

415 Hurst, A. Dyschezia and Megacolon, *Radiology* **42** 128-135, 1944.

416 Delano, P. J., in discussion on Hurst,⁴¹⁵ pp 190-191.

417 Gold, H., and Zahm, W. A Method for the Evaluation of Laxative Agents in Constipated Human Subjects, with a Study of the Comparative Laxative Potency of Fumarates, Sodium Tartrate and Magnesium Acid Citrate, *J Am Pharm A* **32** 173-178, 1943.

combined opaque enema and air inflation method is particularly helpful in diverticulosis, with other lesions this method may be misleading. Poppel and Bercow⁴²⁶ describe a modified barium sulfate mixture, consisting of 75 Gm of barium sulfate and 5 Gm of acacia in 2 quarts (1.9 liter) of water, which permits the demonstration of not only the contour, as with the ordinary barium enema, but of the normally distended lumen and its contents. The method is considered of value particularly in the study of the region of the flexures and in cases in which there is considerable redundancy. Polyps and diverticula are more easily seen than with the ordinary barium sulfate enema. Wissing and Lowman⁴²⁷ emphasize the importance of the lateral view, particularly in the sigmoid and lower descending colon.

Enteritis and Hepatitis—Pollack and Gerber,⁴²⁸ in a study of 88 cases of primary hepatic disease, found phlegmonous inflammation of the small or large intestine in 18. The lesion, apparently not previously described, has not been encountered by the authors in the past ten years except in association with primary disease of the liver, cirrhosis or toxic necrosis. The mechanism of production and the clinical significance are not yet clear. The intestine appears decidedly boggy. On microscopic examination there is "seen a diffuse phlegmonous inflammation of the intestinal wall characterized by an infiltration of all the layers of polymorphonuclear leukocytes." The lesions do not appear to bear a direct relation to the degree of hepatic inflammation.

Cecitis—Spivack and Busch⁴²⁹ report 2 cases of phlegmonous cecitis and collected 35 cases from the literature with a mortality of 8 per cent. Two types are described, circumscribed and diffuse. Phlegmonous cecitis is presented as a distinct disease entity attributed to enterogenous or hematogenous infection. The former is considered the more common and to result from mucosal abrasions from hard fecal masses, intestinal parasites or foreign bodies. Zieman⁴³⁰

reports a case of foreign body, apparently a fish bone, perforating the cecum, with uneventful recovery following operation.

Rosser⁴³¹ reports 2 cases of simple ulcer of the cecum not associated with other recognized infections or tumefactions of the bowel. Less than 50 such cases have been described. The ulcer is usually found near the ileocecal valve on the mesial side of the cecum, it has a pronounced tendency to perforate and to cause extensive scarring and contraction. The symptoms are variable but usually suggest either appendicitis or cancer of the cecum and thus lead to surgical intervention. Frank and Doughty, in the discussion of this paper, each describe similar cases.

Nonspecific Ulcerative Colitis—Alvarez and Baigen⁴³² emphasize the value of the sedimentation rate in the recognition of diarrhea due to organic disease. If the figure is low there is little chance that organic disease will be found, while if it is high, more than 40 or 50 mm (Westergren method), there is almost certainly something seriously wrong with the bowel. They have also found the sedimentation rate helpful in estimating the extent or seriousness of colitis of the "thrombolytic" variety. In patients in whom only the rectum and sigmoid segment are involved, the rate may be within normal limits.

An extract from the liver and lungs of patients with nonspecific ulcerative colitis contained a substance toxic and often lethal for mice.⁴³³ Such a toxic factor was found in lesser amounts or in a milder form in an occasional control extract of stillborn infants but not in adult control lungs or infant livers.

An extensive study of patients with chronic ulcerative colitis disclosed that the majority had abnormal reactions to oral dextrose tolerance tests and that none of the reactions to intravenous dextrose tests were normal, although metabolism of dextrose as determined by basal metabolic rates and respiratory quotients was essentially normal.⁴³⁴ A relatively small per cent of the patients had low fasting plasma vitamin A, carotene and vitamin C levels. The prothrombin clotting time was prolonged in the majority of

426 Poppel, M. H., and Bercow, C. The Use of a Modified Opaque Barium Sulfate Mixture in the Roentgenology of the Colon, *Am J Roentgenol* **51** 727-729, 1944.

427 Wissing, E. G., and Lowman, R. M. The Lateral View in the Roentgenologic Diagnosis of Lesions of the Colon, *New England J Med* **229** 207-210, 1943.

428 Pollack, A. D., and Gerber, I. E. Abdominal Visceral Lesions Associated with Primary Disease of the Liver, *Arch Path* **36** 608-611 (Dec) 1943.

429 Spivack, A. H., and Busch, I. Phlegmonous Cecitis. Report of Two Cases and a Review of the Literature, *Am J Surg* **61** 54-59, 1943.

430 Zieman, S. A. Perforating Foreign Body of the Cecum, *U S Nav M Bull* **41** 1103-1105, 1943.

431 Rosser, C. Simple Penetrating Ulcer of the Cecum, *Ann Surg* **119** 377-383, 1944.

432 Alvarez, W. C., and Baigen, J. A. The Value of the Blood Sedimentation Rate in Recognizing Diarrheas Due to Organic Disease, *Proc Staff Meet, Mayo Clin* **19** 255, 1944.

433 Steiner, P. E., Stanger, D. W., and Bolyard, M. A Toxic Factor in the Tissues in a Case of Nonspecific Ulcerative Colitis, *Proc Soc Exper Biol & Med* **55** 8-10, 1944.

434 Bercovitz, Z., and Page, R. C. Metabolic and Vitamin Studies in Chronic Ulcerative Colitis, *Ann Int Med* **20** 239-254, 1944.

the patients. The results were all taken as evidence that the syndrome of chronic ulcerative colitis is not confined to an altered physiology of the colon but is also manifest by altered absorption and utilization, impairment of the insulin mechanism, generalized decreased capillary resistance and altered blood coagulation due to a decrease in prothrombin content.

Peters⁴³⁵ reports chronic ulcerative colitis with complications including abdominal fistula, carcinoma of the cecum, renal insufficiency and pigmentation of the skin suggesting Addison's disease.

Sauer and Bargen⁴³⁶ report 26 cases of ulcerative colitis complicated by carcinoma, thus bringing to 50 the number of such cases reported from the Mayo Clinic, an incidence of carcinoma of 25 per cent. In this group of 26, polyps were present in 15 (58 per cent). There were multiple carcinomas in 8, the greatest number in 1 person being eight primary carcinomatous lesions, all large enough to be diagnosed on roentgenologic examination.

Drueck,⁴³⁷ on the basis of 3 cases of ulcerative colitis (1 of acute, 1 of chronic and 1 of recurrent colitis), advocates the use of iodoxyquinoline sulfonic acid in 2 per cent solution for colonic irrigation, and 4 to 8 grains (given by mouth) every six hours. Litvak and Levy⁴³⁸ report a case of ulcerative colitis in a girl, aged 8½ years, in whom they thought quick improvement was brought about by the use of chiniofon. We recall, however, that over the past two decades chiniofon has been used extensively in treatment of this disease and abandoned.

Two fatalities in cases of chronic ulcerative colitis after an ileostomy are attributed to perforation of the ileum followed by peritonitis, hence it is suggested that ileostomy, if indicated, be performed at least 90 cm above the ileocecal valve.⁴³⁹ Peelen and Yonkman⁴⁴⁰ describe severe diarrhea of the small intestine from an ileostomy. As therapy bismuth and opium were given orally.

435 Peters, G. A. Chronic Ulcerative Colitis with Unusual Complications. Report of Case, Proc Staff Meet, Mayo Clin **19** 303-307, 1944.

436 Sauer, W. G., and Bargen, J. A. Chronic Ulcerative Colitis Followed by Carcinoma. Report of Twenty-Six Cases, Proc Staff Meet, Mayo Clin **19** 311-316, 1944.

437 Drueck, C. J. Treatment of Chronic Ulcerative Colitis, Am J Digest Dis **11** 10-12, 1944.

438 Litvak, A. M., and Levy, H. Non-Specific Ulcerative Colitis—Case Report and Review of the Literature, Arch Pediat **61** 293-299, 1944.

439 Crandon, J. H., Kinney, T. D., and Walker, I. J. Perforation of the Ileum Following Late Ileostomy for Ulcerative Colitis, New England J Med **230** 419-421, 1944.

440 Peelen, M., and Yonkman, F. F. Tannin Control of Ileostomy, Am J Digest Dis **10** 277-278, 1943.

without effect. A dramatic response apparently followed the administration of acetyl tannic acid and albumin tannate given in doses of 1 Gm every four hours.

Miller⁴⁴¹ describes methemoglobinemia from bismuth subnitrate used in treatment of chronic ulcerative colitis. In forty-eight hours after use of the drug was stopped the level of methemoglobin in the blood decreased 80 per cent.

Amebiasis — Diaz-Rivera and Rasberry⁴⁴² attribute the low reported incidence of amebiasis in Philadelphia to insufficient stool examinations and, until recently, lack of interest. Bews and Choquette⁴⁴³ surveyed 500 unselected patients admitted to the Military Hospital at Ste Anne de Bellevue, Quebec, and showed that 236 (47.2 per cent) of these had some form of protozoal cyst. Food handlers may be effective transmitters of the organism. Sawitz⁴⁴⁴ recommends that before the diagnosis of amebiasis is excluded three stool specimens passed on alternate days should be examined followed by the examination of a stool after a saline cathartic and the examination of material obtained from the sigmoid on sigmoidoscopy. The unstained or hematoxylin-stained fecal film technique supplemented by the zinc sulfate centrifugal flotation method are recommended.

Continuous infection of children with amebiasis in a children's home suggested that the method of transmission of the infection was direct contact transfer aided by the general pollution of the environment.⁴⁴⁵ Live steam sterilization of the environment combined with mass antiamebic chemotherapy constituted a simple and practical means of controlling the infection.

Jackman and Cooper⁴⁴⁶ proctoscopically found ulceration of the amebic type in the lower part of the bowel in 20.8 per cent of 115 patients with amebiasis. Biopsy and scrapings from the ulcer at the time of proctoscopy afforded a positive diagnosis in 2 cases in which repeated examina-

441 Miller, R. C. Methemoglobinemia Occurring in a Case of Chronic Ulcerative Colitis, Proc Staff Meet, Mayo Clin **19** 308-311, 1944.

442 Diaz-Rivera, R. S., and Rasberry, E. A. Amebiasis. Analytical Study of Cases Admitted to a Philadelphia Hospital During the Last Five Decades, Am J M Sc **207** 754-755, 1944.

443 Bews, D. C., and Choquette, L. P. E. A Preliminary Study of the Incidence of the Intestinal Protozoa in the Canadian Armed Forces, Canad M A J **49** 501-503, 1943.

444 Sawitz, W. G. The Diagnosis of Amebiasis, Clinics **2** 828-841, 1943.

445 Ivanhoe, G. L. Studies on the Transmission of Amebiasis in a Children's Home in New Orleans, Am J Trop Med **23** 401-419, 1943.

446 Jackman, R. J., and Cooper, W. L. Value of Proctoscopy in the Diagnosis of Amebiasis, Am J Digest Dis **10** 365-366, 1943.

tions of the stools had given negative results. Anal inflammatory lesions, such as abscess and fistula, occurred in only 17 per cent of the cases, in striking contrast with the high percentage of such lesions observed in cases of chronic ulcerative colitis and regional ileitis. The importance of a proctoscopic examination to rule out other disease, such as neoplasm, occurring independent of the amebiasis is indicated by the finding in 1 case of a carcinoma in the lower sigmoid in a patient who had not improved clinically after amebicidal therapy.

Jorge⁴⁴⁷ and his collaborators report acute amebic abscess of the liver and acute peritonitis due to intestinal perforation. Dysentery had been present three years before the onset of the acute illness. Results of examinations of stools were negative for organisms but amebas were found in the wall of the abscess. In spite of intensive treatment with emetine hydrochloride and sulfa-pyridine, vioform and arsenicals, as well as surgical drainage of the abscess, perforation of the colon occurred, leading to death from acute peritonitis. Numerous ulcerations were found in the colon. Trophozoites were present in the walls of the intestinal ulcerations.

The successful local treatment with penicillin of an amebic abscess of the liver secondarily infected with beta hemolytic streptococci of Lancefield group G is described⁴⁴⁸.

Other Parasites—Raifman⁴⁴⁹ reports another case of infection with *Isospora bigemina*, also described by Bustos. The patient was treated, with good results, but we must point out that such infections are known to be self limited.

Lowe,⁴⁵⁰ in reporting 16 cases of human infection with *Strongyloides stercoralis*, found that gentian violet medicinal gave symptomatic relief, but neither it nor the other drugs tried, emetine hydrochloride, fuadin (stibophen) and antimony and potassium tartrate, could be considered satisfactory agents for eradicating the infection.

Wallace and Chamberlin⁴⁵¹ report that in the treatment of hookworm infection tetrachloro-

ethylene administered orally is satisfactory in the majority of cases. Intraduodenal administration gives better results but should be reserved for refractory cases, because the oral method is usually satisfactory and the intraduodenal method is time consuming. Lowe⁴⁵² studied 363 cases of mild hookworm infection in patients with malaria. When the eosinophil count was greater than 1350 cells per cubic millimeter helminth infection was almost certainly present. Cutaneous lesions, dyspepsia and pronounced eosinophilia without anemia were produced by the hookworm infection, in contrast with the manifestations of malaria.

Hsu⁴⁵³ examined stool specimens from 720 persons in northwest China. The lowest incidence of infection with helminths was 40.21 per cent and the highest 70.42 per cent, the majority of the parasites were *Ascaris lumbricoides*. The highest incidence of *Endamoeba histolytica* infection was 2.43 per cent.

Fernando and Balasingham⁴⁵⁴ review 162 cases of acute ascariasis. The mortality was 27 per cent in patients with ascariasis alone and 50 per cent in patients in whom ascariasis was complicated by other diseases. Acute symptoms followed anthelmintic therapy in 18 per cent of cases. Symptoms of acute gastroenteritis were the presenting feature in 53 per cent and those of an "acute abdomen," chiefly partial intestinal obstruction, in 20.9 per cent. The acute gastroenteritis or partial obstruction should be treated before anthelmintic therapy is given.

Most⁴⁵⁵ found phenothiazine in doses of 30 mg per kilogram of body weight given for three days an effective drug in the treatment of human *Enterobius vermicularis* infection but ineffective against infections with *Ascaris lumbricoides*, *Necator americanus*, *Strongyloides stercoralis* and *Trichocephalus*. The drug was safe in therapeutic dosage, but toxic doses resulted in hemolytic anemia and hepatitis.

Elliott⁴⁵⁶ also recommends phenothiazine.

Sisk⁴⁵⁷ emphasizes that when one member of a household is infected with pinworms all other

447 Jorge, J. M., Goñi Moreno, I., and Peralta, A. R. Consideraciones sobre un caso de amebiasis grave, *Rev. Asoc. méd. argent.* **57**: 707-709, 1943.

448 Noth, P. H., and Hirshfeld, J. W. Amebic Abscess of the Liver with Secondary Infection. Local Treatment with Penicillin, *J. A. M. A.* **124**: 643-646 (March 4) 1944.

449 Raifman, J. A Case of Human Parasitosis Caused by the *Isospora Bigemina*, *Rev. Gastroenterol.* **10**: 279-282, 1943.

450 Lowe, T. E. Strongyloidiasis in Man. Infestation with *Strongyloides Stercoralis* (Bavay, 1876), *M. J. Australia* **1**: 429-435, 1944.

451 Wallace, W. C., and Chamberlin, D. T. Hookworm Infestation. Comparative Methods of Treatment, *Mil. Surgeon* **93**: 427-432, 1943.

452 Lowe, T. E. Hookworm Infestation, *M. J. Australia* **1**: 289-292, 1944.

453 Hsu, K. C. Human Intestinal Parasites in Northwest China. A Brief Survey, *Chinese M. J.* **61**: 292-295, 1943.

454 Fernando, P. B., and Balasingham, S. Acute Ascariasis in Children, *Indian J. Pediat.* **10**: 149-173, 1943.

455 Most, H. Studies on the Effectiveness of Phenothiazine in Human Nematode Infections, *Am. J. Trop. Med.* **23**: 459-464, 1943.

456 Elliott, M. Phenothiazine in the Treatment of Human Intestinal Helminthic Infestations, *Tr. Roy. Soc. Trop. Med. & Hyg.* **37**: 163-164, 1944.

457 Sisk, W. N. The Modern Treatment of Pinworm Infections, *North Carolina M. J.* **5**: 52-55, 1944.

members can usually be shown to be infected if one uses the cellophane swab technic. A minimum of seven swabs should be examined before one can be reasonably sure that the patient is not infected. Sisk has never succeeded in ridding a household of pinworms when one or more members refused to take the treatment. Treatment with gentian violet medicinal is reasonably satisfactory provided it does not cause too much nausea. Phenothiazine gives results equal, if not superior, to those obtained with gentian violet, although it also is somewhat toxic and must be used with care. Whichever treatment is used, the only way to be certain of cure is to take at least seven swabs from each member of the family, three about one week after treatment and four more two weeks later. About 60 per cent of the families will be cured on the first treatment, about half of the remaining 40 per cent on the second treatment and the remaining 20 per cent on the third treatment if it is taken.

Megacolon—McKell⁴⁵⁸ reports 2 cases of so-called anal achalasia with megacolon in which symptomatic relief was obtained with neostigmine and ergotamine tartarate administered orally. Hawksley⁴⁵⁹ reports 12 cases of Hirschsprung's disease in children from 2 to 11 years of age treated with spinal (nupercaine) anesthesia repeated two or three times. Six patients were cured, 5 improved and in 1 no modification was observed.

In a careful analysis of congenital megacolon, the cases of 29 patients on whom subtotal colectomy was performed are reported, of these, 24 were males⁴⁶⁰. Seven of the 29 (24.1 per cent) died as a result of the operation. Follow-up studies were made on 16, the results being considered excellent in 13 and good in 3. Subtotal colectomy is considered the treatment of choice in cases of segmental congenital idiopathic megacolon due to chronic mechanical obstruction. It is also indicated for persons with severe megacolon, for persons not responding to spinal anesthesia, and for male patients. Except in emergencies it is contraindicated for infants. Johnson and Benson⁴⁶¹ report megacolon in a

boy aged 2 years, observed proctoscopically to have a stricture of unknown origin 10 cm above the anus, narrowing the lumen to 3 mm. The megacolon disappeared after removal of the stricture. Martin and Ward⁴⁶² report a case of megacolon in which volvulus necessitated resection of the transverse colon followed by resection of the remainder of the colon for an associated inflammatory stricture of the sigmoid and anastomosis of the terminal portion of the colon.

Obstruction—Zaslow⁴⁶³ reports obstruction of the large bowel in 2 newborn infants due to congenital bands extending from the under surface of the liver to the hepatic flexure of the colon and calls attention to the similarity of the symptoms to those of obstruction of the large bowel in adults, namely, abdominal distention out of proportion to the amount of vomiting. Bueermann⁴⁶⁴ and Dennis⁴⁶⁵ give brief discussions of the diagnosis and surgical management of obstructive lesions of the colon.

Traumatic Rupture—Cameron⁴⁶⁶ and associates made an interesting and well illustrated study of the abdominal injuries due to under-water explosion. Twenty patients were submitted to operation, with a mortality of 50 per cent. Retroperitoneal and subserous hemorrhages occurred in all patients. Perforation of the cecum was present in 9 and of the ileum in 7, and multiple perforations were present in 4. Late perforations occurred in 2, a result probably of hemorrhage initiated by the primary injury. A late survey of 80 who recovered without operation showed that the commonest symptom was abdominal pain persisting from three days to three months. Melena was present in 82 per cent of these patients and in some persisted for four months. In 20 per cent a history of hemoptysis was reported, and in 14 per cent, hematemesis. An experimental investigation with 16 goats was made. Eight of them had their chest and abdomen immersed and 8 had only the abdomen immersed. Intestinal lesions were common in both types. Bleeding by

458 McKell, J. Anal Achalasia with Megacolon in Children Treated Successfully with "Prostigmin" and Ergotamine Tartrate, *M J Australia* **1** 465-466, 1944.

459 Hawksley, M. Spinal Anaesthesia in the Treatment of Hirschsprung's Disease with Reports of Twelve Cases, *Brit J Surg* **31** 245-252, 1944.

460 Whitehouse, F., Borgen, A. J., and Dixon, G. F. Congenital Megacolon. Favorable End Results of Treatment by Resection, *Gastroenterology* **1** 922-937, 1943.

461 Johnson, J. R., and Benson, R. E. The Surgical Treatment of Megacolon with Report of a Case of Acquired Megacolon, *Proc Staff Meet, Mayo Clin* **19** 324-328, 1944.

462 Martin, J. D., Jr., and Ward, C. S. Megacolon Associated with Volvulus of the Transverse Colon, *Am J Surg* **64** 412-416, 1944.

463 Zaslow, J. Obstruction of the Large Bowel in Newborn Infants Due to Congenital Bands, *J Pediat* **23** 337-339, 1943.

464 Bueermann, W. H. Obstructive Lesions of the Colon. Diagnosis and Surgical Management, *Northwest Med* **42** 311-315, 1944.

465 Dennis, C. Treatment of Large Bowel Obstruction. Transverse Colostomy. Incidence of Incompetency of Ileocecal Valve, Experience at the University of Minnesota Hospitals, *Surgery* **15** 713-734, 1944.

466 Cameron, G. R., Short, R. H. D., and Wakeley, Cecil P. G. Abdominal Injuries Due to Under-Water Explosion, *Brit J Surg* **31** 51-66, 1943.

rectum and mesenteric hemorrhages were more severe when the abdomen alone was immersed. Gill and Hay,⁴⁶⁷ in a series of 16 such cases, operated on 6 patients, 4 of them dying. Two of the remaining patients died without operation. Martin⁴⁶⁸ reports the bizarre case of a 28 year old seaman thrown into the water after a cruiser was torpedoed. A depth charge exploded near him. Perforation of the rectum occurred as a primary event in a single organ, with no evidence of other abdominal injury. Death from peritonitis ensued.

Hicken and Carlquist⁴⁶⁹ discuss rupture of the gastrointestinal tract due to nonpenetrating injuries, report 6 cases and emphasize the frequency with which this condition occurs. Delayed perforation occurred in 60 per cent of the cases and was not recognized until peritonitis occurred. Collins⁴⁷⁰ reports 3 more cases, further illustrating the necessity of careful observation and early exploration. Brown⁴⁷¹ reports a spontaneous perforation of the pelvic colon, and Swenson and Harkins⁴⁷² describe traumatic rupture of the rectum caused by compressed air.

Seybold, Black and Jackman,⁴⁷³ in discussing injuries to the rectum by impalement, describe the case of a 3 year old boy who had sat down forcibly on the shank of a bicycle seat. Proctoscopic examination disclosed a hole in the anterior wall of the rectum in the region of the rectovesical space. This was repaired through an abdominal incision. Five grams of sulfathiazole crystals were placed in the pelvis. Combined gas gangrene and tetanus antitoxin was given intramuscularly. The child made an uneventful recovery. Of 7 such patients treated in the presulfonamide era, 2 died and 5 recovered.

Diverticulitis—Young and Young⁴⁷⁴ review the literature and analyze 84 cases of diverticu-

litis. Casper,⁴⁷⁵ in 489 studies with barium sulfate enema observed 5 cases of localized irritability and spasticity of the proximal portion of the sigmoid, interpreted as a localized inflammation and thought to represent a clinical entity. In the single fatal case, death resulted from peritonitis. Autopsy showed the walls of the rectum, sigmoid and distal descending colon noticeably thickened, edematous, grayish red and friable. No definite ulcerations were seen. The roentgenograms in the 5 cases are all suggestive of either diverticulitis without demonstrable diverticula or so-called nonspecific ulcerative colitis, leading Casper to question the existence of sigmoiditis as an entity. Thunig⁴⁷⁶ reports diverticulitis of the sigmoid complicated by perforation mistaken for carcinoma and successfully resected, with subsequent reestablishment of the continuity of the colon.

Lymphogranuloma Venereum—Seidenstein⁴⁷⁷ concludes that anorectal manifestations of lymphogranuloma seem to be best treated by prolonged systemic and local therapy with sulfonamide drugs combined with at least one course of Frei antigen intravenously. Napp⁴⁷⁸ presents an interesting study of the disease. Bodkin⁴⁷⁹ attributes the difficulty in the passage of stools to the prolapse of the rectal wall into the stricture on straining and describes a surgical procedure for its correction.

Polyposis—McLaughlin⁴⁸⁰ reviews diffuse polyposis and collected 30 cases in the literature between 1937 and 1942, bringing the total number of such cases to 331. David,⁴⁸¹ in emphasizing the importance of destroying or removing polyps, states that many can be handled by fulguration or local removal but more radical surgical measures may be indicated. Keller⁴⁸² describes an instance in which local excision of a degenerated polyp on the posterior wall of the lower part of the rectum effected an apparent cure.

467 Gill, W. G., and Hay, C. P. A Clinical Study of Injuries of the Abdomen Due to Under-Water Explosion, *Brit J Surg* **31** 67-73, 1943.

468 Martin, P. G. C. Perforation of Rectum from Immersion Blast, *Lancet* **2** 605-606, 1943.

469 Hicken, N. F., and Carlquist, J. H. Traumatic Rupture of the Gastro-Intestinal Tract by Non-Penetrating Forces, *Am J Surg* **64** 209-216, 1944.

470 Collins, A. N. Traumatic Rupture of the Intestine, *Minnesota Med* **27** 276-278, 1944.

471 Brown, J. Spontaneous Perforation of the Pelvic Colon, *Brit J Surg* **31** 307-308, 1944.

472 Swenson, S. A., Jr., and Harkins, H. Rupture of the Rectosigmoid by Compressed Air. Case Report, *Am J Surg* **63** 141-143, 1944.

473 Seybold, W. D., Black, B. M., and Jackman, R. J. Impalement of the Rectum, *Proc Staff Meet, Mayo Clin* **19** 224-227, 1944.

474 Young, E. L., and Young, E. L., III. Diverticulitis of the Colon. A Review of the Literature and an Analysis of Ninety-One Cases, *New England J Med* **230** 33-38, 1944.

475 Casper, S. L. Sigmoiditis, *Am J Roentgenol* **50** 24-32, 1944.

476 Thunig, L. A. Complicated Diverticulitis of the Sigmoid. Case Report, *Am J Surg* **64** 386-399, 1944.

477 Seidenstein, H. R. Rectal Stricture Due to Lymphogranuloma Venereum, *Surgery* **14** 73-82, 1943.

478 Napp, O. E. Estrechez linfogranulomatosa rectosigmoidea, *Prensa med argent* **30** 2224-2234, 1943.

479 Bodkin, L. G. Stricture of the Rectum, *Am J Surg* **61** 277-279, 1944.

480 McLaughlin, C. W., Jr. Diffuse Polyposis of the Large Intestine, *Am J Surg* **62** 258-266, 1943.

481 David, V. C. The Management of Polyps Occurring in the Rectum and Colon, *Surgery* **14** 387-394, 1943.

482 Keller, D. R. Carcinoma of the Rectum, *Am J Surg* **64** 346-351, 1944.

Endometriosis — Ben-Asher⁴⁸³ reviews the literature of endometriosis of the rectosigmoid, discusses the pathology, diagnosis, roentgenologic manifestations and treatment and reports the case of a 37 year old woman who gave a history of periodic pains in the lower part of the abdomen associated with diarrhea, aggravated during the menstrual period, followed by obstipation with ribbon-like stools. Sterility and menstrual disorders were present. On sigmoidoscopic examination an obstruction was found at about 6 inches (15 cm) but without a lesion of the mucosa. The barium sulfate enema showed a constant filling defect in the region of the sigmoid, with regular borders and an intact but puckered mucosa. At the operation a mass was found involving the entire circumference of the bowel for 1½ inches (3.8 cm), an endometrial cyst of the ovary and endometriosis of the mesovarium. The uterus, both ovaries and both tubes were removed, nothing was done with the tumor of the sigmoid. Three years later the patient was reported as having gained 24 pounds (10.9 Kg) in weight, and a barium enema disclosed no evidence of a filling defect of the sigmoid. Smith,⁴⁸⁴ on the other hand, reports a patient treated by resection of the involved colon followed by castrating doses of high voltage roentgen therapy.

Carcinoma — Cave⁴⁸⁵ notes that the Bureau of Vital Records and Statistics of the city of New York, with a population of 7,300,000 in the year 1942, showed that 1,962 persons died from cancer of the stomach, 1,616 died of cancer of the colon and 911 of cancer of the rectum. The value of the more frequent use of the sigmoidoscope and the x-ray for patients with the slightest suspicion of a disturbed gastrointestinal tract is emphasized.

Seefeld and Bargaen⁴⁸⁶ studied with extreme care the lymphatic, perineural and venous spread of 100 specimens of rectal carcinoma resected at Mayo Clinic during the years 1935 and 1936, finding lymphatic invasion in 47 per cent of the cases, perineural invasion in 30 per cent, and venous invasion in 20 per cent. The incidence of invasion increased with the degree of malignancy. Metastasis to lymph nodes was observed in 67 per cent of the cases with perineural in-

volvement and in 85 per cent of those with venous involvement. Pain was a prominent symptom in 89 per cent of the cases with perineural invasion. Local recurrence was found in 27, with neural involvement in 22.7 per cent, venous involvement in 11.1 per cent, involvement of both sorts in 25.9 per cent and of neither sort in 40.7 per cent. In 4 cases of local recurrence, metastasis to lymph nodes occurred without invasion of nerves or veins and in 7 cases without histologic evidence of spread by any of the three routes. Visceral metastatic lesions were present at operation or developed later in 94 per cent of the cases with venous involvement, whereas they were found in only one fifth of this frequency in cases without venous invasion. Singleton⁴⁸⁷ gives a good description of the blood supply, and Whipple⁴⁸⁸ outlines the surgical treatment of the terminal ileum, cecum and right colon.

Connor and Harvey,⁴⁸⁹ in analyzing the important symptoms and signs in 50 cases of carcinoma of the right side of the colon, found abdominal pain and weakness common symptoms. Occult blood was seen in the stools in 75 per cent of the cases, and a palpable tumor was noted in 82 per cent. In 8 cases the diagnosis was not made preoperatively.

Bertin⁴⁹⁰ concludes that metastasis from cancer of the digestive tract to bone is more common than is generally realized, the bones of the trunk being the most frequent sites. The lesions are usually osteolytic and may obtain considerable size before producing symptoms. Roentgen therapy had no effect in the 3 cases described. Beilin⁴⁹¹ reviews the features of 117 cases of cancer of the rectum. Guzman⁴⁹² reports that lymphogranuloma was associated with cancer of the rectum and genitals in 8 of 12,546 cancerous patients observed during a ten year period. One case is described in which the rectum and vulva were involved by both diseases.

The incidence of multiple malignant lesions has been reported to be between 3 and 5 per cent.

483 Ben-Asher, S. Endometriosis of the Rectosigmoid. Report of a Case with a Review of the Literature, *Am J Digest Dis* **11** 141-144, 1944.

484 Smith, R. S. Endometrioma of the Sigmoid, *Northwest Med* **42** 192-195, 1943.

485 Cave, H. Cancer of the Colon, *Bull New York Acad Med* **20** 255-263, 1944.

486 Seefeld, P. H., and Bargaen, J. A. The Spread of Carcinoma of the Rectum. Invasion of the Lymphatics, Veins, and Nerves, *Ann Surg* **118** 76-90, 1943.

487 Singleton, A. O. The Blood Supply of the Large Bowel with Special Reference to Resection, *Surgery* **14** 328-341, 1943.

488 Whipple, A. O. Surgery of the Terminal Ileum, Cecum and Right Colon, *Surgery* **14** 321-327, 1943.

489 Connor, G. J., and Harvey, S. C. The Diagnosis of Carcinoma of the Right Colon, *Yale J Biol & Med* **16** 289-300, 1944.

490 Bertin, E. J. Metastasis to Bone as the First Symptom of Cancer of the Gastro-Intestinal Tract. Report of Three Cases, *Am J Roentgenol* **51** 614-622, 1944.

491 Beilin, D. S. Clinical Features, Diagnosis and Treatment of Carcinoma of the Colon and Rectum, *Radiology* **42** 539-544, 1944.

492 Guzman, L. Co-Existence of Chronic Lymphogranuloma and Cancer, *Radiology* **41** 151-156, 1943.

McCormick⁵⁰³ finds that during a three year study many of these are synchronous or multicentric malignant lesions. Multiple asynchronous primary malignant lesions are less frequent. Lichtman⁴⁹³ reports 1 case in which three primary malignant lesions developed in the colon in the course of seventeen years and a second which involved the removal of coincident primary carcinomas of the rectum and lung. Shenfeld and Rudolph⁴⁹⁴ found 2 cases of multiple primary malignant tumors involving the gastrointestinal tract and 1 involving the breast and gallbladder in 128 cases of malignant disease. In 110 surgical specimens of malignant disease of the gastrointestinal tract there were 2 synchronous malignant growths. The 3 cases reported include 1 in which there were two apparently independent carcinomas involving the cecum and the transverse colon. The other 2 cases consist of 1 of squamous cell carcinoma of the esophagus and an adenocarcinoma of the stomach and another of adenocarcinoma of the esophagus and adenocarcinoma of the stomach.

McGauley⁴⁹⁵ discusses the advantage of a high operation rate over the maintenance of a low postoperative mortality rate and shows that from the standpoint of the number of patients alive one year after operation the former is preferable. Allen⁴⁹⁶ thinks that the term "resectability" should be substituted for "operability." In his own series 91 per cent of the lesions were resectable. The mortality and morbidity were directly related to resectability. Of the first 50 patients reported on by Murdock⁴⁹⁷ for whom radical resection of the left side of the colon and the rectum was done only 1 was over 70 years of age and the mortality was 4 per cent. The subsequent acceptance of more patients of advanced age increased the mortality to 9.3 per cent, from which Murdock concludes that a considerable increase in mortality must be expected in the case of patients over 70. Cattell⁴⁹⁸ reports that 81.4 per cent of 172 patients were submitted to resection for carcinoma of the colon and rectum during 1941, with a mortality of 5 per cent. A

one stage abdominoperineal resection was done in 76.7 per cent of the cases of rectal carcinoma, with a mortality of 3.8 per cent. The modified Mickulicz resection was performed for carcinoma of the colon, with a mortality of 2.7 per cent.

Coller and Ransom,⁴⁹⁹ in comparing the results of operation in cases of carcinoma of the rectum observed during the last six years with those observed during the preceding six years, found that operability increased owing to earlier diagnosis, extension of the limits of operability, standardization of the operative technic and improvement in the preoperative and postoperative management. Mayo and Twyman⁵⁰⁰ reported a follow-up study made in 90 cases of carcinoma of the rectum in which the patients survived a one stage combined abdominoperineal resection. At the end of three years 61 of the patients were alive and 29 dead. Eleven operations were considered palliative. Even though obvious metastasis to the liver or deep aortic nodes existed at the time of the operation, 45 per cent of the patients survived three years or more. Dixon⁵⁰¹ describes the technic used in 206 cases of carcinoma low in the sigmoid and the rectosigmoid, 181 of which were performed with a view of cure and 25 as a palliative procedure. The operative mortality rate was reduced from 19.4 to 2.4 per cent. This result was attributed to the careful preoperative treatment. In the operative procedure the superior hemorrhoidal vessels were sacrificed without apparent impairment of the circulation of the rectosigmoid or rectum.

Allen⁵⁰² reports 7 cases of peritonitis secondary to perforation of carcinoma of the colon. Perforations are most likely to occur in the fungating type of adenocarcinoma either at the site of the tumor or in the loop of bowel just proximal. The diagnosis should be suspected for any patient of cancer age who shows evidence of peritoneal inflammation. The treatment is drainage first and resection later, but the prognosis is poor.

493 Lichtman, A. L. Multiple Primary Malignant Lesions, *Proc. Staff Meet., Mayo Clin.* **19**: 317-323, 1944.

494 Shenfeld, W. I., and Rudolph, I. Multiple Primary Carcinomas of the Gastrointestinal Tract, *Surgery* **15**: 579-589, 1944.

495 McGauley, F. F. Carcinoma of the Large Bowel, *New York State J. Med.* **43**: 1727-1731, 1943.

496 Allen, A. W. Carcinoma of Colon, *Surgery* **14**: 350-365, 1943.

497 Murdock, R. L. Cancer of the Left Colon and Rectum, *South. M. J.* **36**: 685-691, 1943.

498 Cattell, R. B. Carcinoma of the Colon and Rectum. A Report of 503 Patients Treated at the Lahey Clinic 1938-1941, Inclusive, *Surgery* **14**: 378-386, 1943.

499 Coller, F. A., and Ransom, H. K. Carcinoma of the Rectum. Conclusions Based on Twelve Years' Experience with Combined Abdominoperineal Resection, *Surg., Gynec. & Obst.* **78**: 304-315, 1944.

500 Mayo, C. W., and Twyman, R. A. One Stage Combined Abdominoperineal Resection for Carcinoma of the Rectum. Results of Three Year Follow-Up Survey in Ninety Cases, *Proc. Staff Meet., Mayo Clin.* **18**: 438-443, 1943.

501 Dixon, C. F. Anterior Resection for Carcinoma Low in the Sigmoid and the Rectosigmoid, *Surgery* **15**: 367-377, 1944.

502 Allen, P. D. Peritonitis Secondary to Perforation in Carcinoma of the Colon, *New York State J. Med.* **43**: 1732-1735, 1943.

503 McCormick, N. A. Cancer of the Rectum, *Radiology* **42**: 531-538, 1944.

period 74 per cent of the patients with rectal cancer were advised to have an abdominoperineal resection, 6 per cent refused. In 80 per cent of those operated on resection was done, in 16 per cent the lesion was too far advanced and in 4 per cent death followed cecostomy for intestinal obstruction. Preoperative roentgen irradiation was usually given. For the patients with inoperable cancer irradiation was used routinely, colostomy was necessary for only 42 per cent of these.

Stenstrom and Malbin⁵⁰⁴ report on 173 patients with cancer of the rectum treated by radiation therapy, 92 of these were inoperable, 12 refused operation, 69 underwent resection but were treated with radiation also because of the likelihood of incomplete removal. Five of the last group were first thought inoperable. Of the patients treated by resection followed by irradiation 34 per cent survived five years or more. Of 104 treated by radiation alone or with colostomy 5 survived five years, the average length of life was twenty-one months.

In dogs 900 r may lead to ulceration and perforation of the rectum⁵⁰⁵. In a review of 195 cases of cancer of the rectum and sigmoid treated by radiation the conclusion is reached that roentgen ray therapy is of value in freeing a fixed cancer preoperatively and as a palliative measure for patients with inoperable cancer.

Carroll⁵⁰⁶ describes a deodorant containing charcoal and phenylsalicylate for use with colostomies.

Lymphosarcoma—Harper, Waugh and Dockerty,⁵⁰⁷ in reporting on lymphosarcoma of the cecum, emphasize that apparently inoperable lesions may be lymphosarcomatous and hence can be treated by resection and irradiation.

504 Stenstrom, K W, and Malbin, M. Results of Treatment of 173 Cases of Carcinoma of the Rectum, *Radiology* **42** 545-549, 1944.

505 Pohle, E A, McAneny, J B, and Lovell, B K. Radiation Therapy in Carcinoma of the Rectum and Sigmoid. An Experimental Study of the "Danger" Dose of Roentgen Rays for the Intestinal Mucosa in Dogs and an Analysis of 195 Cases Treated in the State of Wisconsin General Hospital During 1928-1938, *Radiology* **41** 225-232, 1943.

506 Carroll, W C. A Deodorant for Colostomies, *Minnesota Med* **26** 709-710, 1943.

507 Harper, S B, Waugh, J M, and Dockerty, M B. Lymphosarcoma of the Cecum. Report of Case, *Proc Staff Meet, Mayo Clin* **19** 182-187, 1944.

Winkelstein and Levy⁵⁰⁸ report 15 cases of lymphosarcoma of the intestine, describe the proctoscopic picture and consider the differentiation between small round cell and reticulum cell tumors to be unimportant clinically. Even with surgical removal plus radiotherapy the disease is invariably fatal, the duration of life being usually less than one year, although 1 of their patients lived six years.

Miscellaneous—The literature of fecal fistula is reviewed, with a discussion of its classification, incidence and cause and a report on 590 patients observed at the Mayo Clinic in a twelve year period⁵⁰⁹.

Ducassi and Bagen⁵¹⁰ report the unusual case of a 28 year old woman who gave the history of bleeding from the vagina on one day followed by hemoptysis continuing for one or two days and followed by rectal bleeding, the amount of blood passed by rectum varying from a teaspoonful to a pint (500 cc) at a time. Aside from hemorrhoids no rectal lesion was found.

Pemberton and Brindley⁵¹¹ report on a stenosing superficially ulcerated lesion of the rectum which when resected and examined histologically was found to be inflammatory, with typical noncaseating tubercles. Culture and smears prepared with carbolfuchsin did not demonstrate the presence of tubercle bacilli, but nevertheless the presumptive diagnosis seemed to be primary tuberculosis of the rectum.

Shucksmith⁵¹² discusses the treatment of anorectal conditions in the Army and recommends the use of caudal anesthesia in operative measures for fissure, hemorrhoids, anorectal abscess and fistula. Cantor⁵¹³ on the basis of 32 cases recommends tattoo-neurotomy as the procedure of choice for so-called cryptogenic pernicious pruritus ani.

508 Winkelstein, A, and Levy, M H. Lymphosarcoma of the Intestines. Fifteen Cases, Characteristic Sigmoidoscopic Picture, *Gastroenterology* **1** 1093-1099, 1943.

509 Lichtman, A L, and McDonald, J K. Fecal Fistula, *Surg, Gynec & Obst* **78** 449-470, 1944.

510 Ducassi, E R, and Bagen, J A. Cyclic Bleeding from the Digestive Tract, *Proc Staff Meet, Mayo Clin* **18** 427-429, 1943.

511 Pemberton, J de J, and Brindley, G V. Tuberculosis of the Rectum. Report of Case, *Proc Staff Meet, Mayo Clin* **19** 46-51, 1944.

512 Shucksmith, H S. Common Anorectal Conditions in Army, *J Roy Army M Corps* **81** 269, 1943.

513 Cantor, A J. Pruritus Ani, *Lancet* **1** 692, 1944.

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